IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CIVIL NO. 13-CV-4507(CCC)

IN RE: DEPOMED PATENT LITIGATION

TRANSCRIPT OF
PROCEEDINGS

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Newark, New Jersey
March 10, 2016

B E F O R E:

THE HONORABLE CLAIRE C. CECCHI,
United States District Judge

Pursuant to Section 753 Title 28 United States Code, the following transcript is certified to be an accurate record as taken stenographically in the above-entitled proceedings.

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Official Court Reporter

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W I T N E S S E S

THE COURT: We're ready to proceed. We are ready for day two. Let's discuss exhibits first. Let's get your appearances on the record. I am assuming you were able to talk regarding exhibits and have some sort of agreement with respect to them. Yes?

MR. BEST: Yes.

THE COURT: This is In Re: Depomed on for purposes of trial.

(Whereupon the attorneys entered their appearances)

MR. BEST: So from yesterday I believe that all parties have agreed. Although if it's not the case, please speak up to the following exhibits being entered into evidence PTX829, PTX1563, PTX 1568, PTX 1559 and PTX 1566.

THE COURT: Counsel? Yes.

MR. PATEL: No objections.

THE COURT: Are there any objections to any of those exhibits? Anyone? None. All right. Thank you. They are admitted.

(Exhibits PTX829, PTX1563, PTX1568, PTX1559 and PTX1566 were marked into evidence.)

THE COURT: Any additional ones? Anything?

MR. ALY: For the next witness I just want to put on the record that counsel and I had spoken. There are some large lab notebooks that are in the German language. But

counsel has agreed to use either English translations that had already been produced in the case and not new ones or images of compounds and that will be fine.

THE COURT: And they are fine with you.

MR. ALY: That's fine.

THE COURT: All right. So it seems like you have agreement on this. Is there any wrinkle on that?

MR. ALY: Sounds good to me.

THE COURT: Sounds good to me.

MR. BEST: I think that's right.

THE COURT: Anything else with the exhibits that are coming up at least with the first witness?

MR. ALY: Not that I see so far.

THE COURT: Anything with the demonstratives?

MR. BEST: We do have demonstratives and we will be handing them out shortly.

THE COURT: Do you want to do that so they can take a look at them real quick, see if there's an issue. And also let me know if anything is sealed. As you know we are going to follow the same procedure.

MR. ALY: On the note of sealing while they are getting materials, counsel and I also talked not about sealing but it reminded me to exclude from Gruss, the next witness the testimony after Dr. Buschmann's not here and he won't be for the Buschmann testimony.

THE COURT: Very well. So we've had the exhibits attended to. They are admitted. We discussed what we are going to do in terms of translations for the next witness.

Is there anything that we need to take care of a housekeepingwise before we start? Let's start with the plaintiff's next witness, please.

MR. BEST: Thank you, your Honor. May I call Dr. Helmut Buschmann to the stand.

THE COURT: Yes. Thank you. And we will have Dr. Buschmann sworn.

H E L M U T B U S C H M A N N, sworn and testifies as follows:

DIRECT EXAMINATION BY MR. BEST:

THE COURT: Let's continue.

Q. Good morning, Dr. Buschmann.

A. Good morning.

Q. Would you please introduce yourself?

A. My name is Helmut Buschmann and I am a chemist by training.

Q. Would you please describe for the Court briefly your educational background in that respect?

A. I have studied chemistry at University of the Aachen and following up I have gotten my diploma --

Q. For the benefit of the reporter, could you restate your educational background?

THE COURT: If you could start again.

A. I have studied chemistry at the University of Aachen. After this I have done my diploma thesis which is and along the educational way at this point and after that at the high level I have done my Ph.D. work in organic chemistry at University of Aachen.

Q. Can you explain what the PhD work was about?

A. The title of the PhD work was to look for a specific photochemical reaction: The so called photon reaction, a model reaction to investigate the chemical expectancy of pathways of reaction mechanisms.

Q. As part of that work, did you do an organic chemical synthesis?

A. Yes, this was part of the Ph.D. thesis.

Q. Are you employed by Grunenthal at this time?

A. During my Ph.D. thesis I was not employed at Grunenthal.

THE COURT: I'm just going to stop you one second. I just want to make sure our court reporter is able to get everything down.

THE WITNESS: Absolutely.

Q. Dr. Buschmann, what is your current employment?

A. I have two major employments. One, I am head of chemistry pharmaceutical development and an I.C.U.R.I.S. affairs. And secondly I am managing director of consultants at a company called R B & C research and development consultants

based in Vent, Austria (sic).

Q. Are you employed at all by Grunenthal?

A. I am currently not employed.

Q. Were you employed by Grunenthal?

A. I was employed from May '92 to January 2002.

Q. And what position did you start with at Grunenthal?

A. My first position was head of a laboratory.

Q. What were your responsibilities and roles in that respect?

A. Responsibilities was to guide two technicians in the synthesis of compounds to be tested in the pharmacological department.

Q. Was yours the only such lab at Grunenthal at that time?

A. There were other lab assistants. The total number at this time were five labs in the so called synthetic chemistry department.

Q. And you mentioned two technicians. Were you also involved in actually performing chemical synthesis at the bench?

A. I have also performed chemical synthesis at the bench.

Q. As time passed at Grunenthal, did you take on further roles?

A. Yes, I was appointed to head of this department synthetic chemistry. And afterwards I was appointed to head of chemical research responsible for medicinal chemistry,

combinatorial chemistry, process development and pilot plants.

Q. And while you took on those additional roles, did you continue as head of laboratory?

A. I continued to be head of my laboratory to continue my research.

Q. And did you hold that role until you departed Grunenthal?

A. This is correct.

Q. When you joined Grunenthal in 1992, what was the nature of Grunenthal's business?

A. The nature of Grunenthal's business was to investigate new compounds in the field of pain. But Grunenthal was also active in other other areas, information and other areas therapeutic areas.

Q. What was the principle or product that was on the market from Grunenthal at that time?

A. At this time the main product was Tramadol.

Q. Could we have demonstrative one which I think is slide two in Rob's deck.

Could you explain for the Court what is on the screen?

A. They are the structured formulas of Sobolsky (ph) shown here which is in effect the resume. That means it consists of 1 to 1 pictures of the two enantiomers shown here on the slide.

Q. So, Tramadol as ingested by patients is actually composed of two different compounds. Is that right?

A. Two parent compounds but the complexity of activity of Tramadol is much more because Tramadol is a so called product so that we have also active metabolites.

Q. When was Tramadol discovered?

A. To my best knowledge it was in the early 60s. It was discovered the first time at Grunenthal.

Q. Now, at the time that you began your work at Grunenthal in May 1992, what did you understand your initial assignment or role to be?

A. I was asked to synthesize compounds, which potential energies they get activity.

Q. Can we have DTX1027 on the screen?

Dr. Buschmann, are you familiar with this document?

A. Yes, I'm familiar with this document.

Q. And of course you have a copy in your binder if you wish to refer to that. And to be clear we've also supplied you with a copy of the German language originally which is PTX 460 for your reference to the extent you have any need for it.

What is this document?

A. This document is a summary of the achievements into so called Tramadol successor project.

Q. Were reports such as this made and kept in the normal course of business at Grunenthal?

A. It was done on a regular basis and to make and to create some successor projects reports.

Q. When did you first see this document?
A. I saw it during the first days I started my work at Grunenthal in May '92.
Q. What is your understanding of what the Tramadol successor project was?
A. At this time my understanding was to look for compounds which have the same pharmacological activity and the complex Tramadol molecule including the activity of metabolites.
Q. Do you have an understanding of how long the Tramadol successor project had been going on before you began your work at Grunenthal?
A. I have no recall because this document was from '91. And to my best knowledge it started somewhere in the '80s.
Q. Could we have page ending in Bates 46362. And could we blow up the first paragraph.
And just looking at the first paragraph, does that refresh your recollection as to when the Tramadol successor project at least in this instance in substantiation began?
A. Yes.
Q. When was that?
A. It was in 1988.
Q. By the time of this document which I believe you mentioned was 1991, about how many new compounds was synthesized as a part of the project?
A. As mentioned here around 550 compounds were synthesized

and tested.

Q. What did you understand the goal or goals of the Tramadol successor project to be?

A. The goal was to find molecules which should have superior activity than Tramadol and combining the complex pharmacological activity without being a resonant, without being a protract.

Q. And if we could go back to 357, in this document, I think it's five pages back, the ten commandments, could you explain for the court what this section discusses?

A. This section was summarizing items of a potential successor molecule based on the knowledge of the Tramadol activity.

Q. Did these items dictate to Grunenthal or tell Grunenthal what the structure of the compounds that should be made would be?

A. This items are just summarizing the pharmacological activity and the profile of the molecule without having any information about potential structural features.

Q. And if we could turn forward to page ending on 361 and focus on those two paragraphs, do you see the section entitled the dual concept.

Could you please explain what the dual concept was in this context?

A. This was an understanding of the pharmacological

activity of the Tramadol. That activity to treat pain was based on two basic mechanism of action. On one hand it's an opioid activity. In addition also the theramine (sic) optic in the patient was considered one of the relevant parts of the overall activity of Tramadol.

Q. And if you could look at the first sentence of the second paragraph which has been highlighted, could you explain for the court what that means?

A. Here it's summarized that these findings at this time were based on in vitro methods. And the translation aspect, if this could be achieved also in the clinical sense was questioned.

Q. Did you know at this time or at the time that you began at Grunenthal, whether you would be able to successfully pursue this strategy to completion?

A. This was not known at this time. This was a challenge.

Q. Now, do you have an understanding whether Grunenthal was the only company attempting to develop new analgesics at this time?

A. In the analgesics field other companies were active at this time.

Q. And do you have an understanding whether other companies were pursuing compounds with multiple mechanisms of action at this time?

A. This was not known at this time.

Q. And when you say this was not known, could you explain what you mean?

A. So, they all populated the information all the information from the databases. Scientific databases were collected to investigate what was the other activity of the other companies.

Q. And was Grunenthal's choice to pursue a compound having multiple mechanisms of action a risky strategy in your view at this time?

A. At this time it was a quite risky strategy because most of the pharmaceutical companies were focusing on their activity means to have one target with one molecule to treat one disease.

Q. And why would that have been the focus? Why would that have been advantageous?

A. Because that to increase activity was to consider minimizing potential side effects of drugs. And based on the technologies arising combinatorial chemistry in screening. It was in one target to just test and compounds optimized to highest community to this target.

Q. I would like to talk a little bit about how Grunenthal and you were pursuing this strategy.

First off Grunenthal could we see Page 43632 the structure which is becoming familiar to the Court, I expect.

THE COURT: It is.

Q. Could you explain for the Judge what is depicted here?
A. Yeah, it is summarized based on the structure of Tramadol what features may be important for synthesizing analogs.
Q. And what is your understanding of what circle A indicates?
A. Here it indicated that aromatic ring system was considered as important but it was considered that one aromatic ring system with different substitutions or more than one aromatic ring sample diastereomeric ring for diastereomer and any other aromatic ring system.
So it's indicating that the aromatic function was considered as important.
Q. And at a high level could you explain what you mean by different substitutions of the aromatic ring?
A. Here for example there's the substitution in the sample A position O.C 3 group is shown but other positions of this aromatic ring system were considered to be investigated.
Q. Focusing now on circle B, could you explain what is shown there?
A. Here nitrogen is shown of the Tramadol molecule and the other lines are indicating that it was considered as important to have a so called tertiary and minor function at this position. That means that at least three different substitutions should be attached to the nitrogen atom. The

meaning is that you have not had the hydrogen place attached to the nitrogen atom.

Q. And did circle B indicate that all the compounds that Grunenthal should synthesize should have this structure, this what is particularly depicted in this circle?

A. No. The meaning was that different substitutions should be attached, investigated to the nitrogen atom not only limited to the messy groups indicated by the other lines here.

Q. Now, focusing on circle C, could you please explain for the court what is shown here?

A. Circle C is a little bit more complex. On one hand here it's considered that's cyclic ring structure was considered as a quite important feature. It also means that different substitutions could be attached to this cyclic ring system and of course also different sizes of the cyclic ring system were considered as potential options.

However, the cyclic ring system was considered as a main important feature to keep the so called configuration of the other substitutions in a fixed, in a fixed arrangement. That means the flows and confirmation was considered as important to have an optimal interaction with the receptor.

Q. And when you have interaction with the receptor, could you explain a little bit more what you mean by that?

A. If you have a molecule which is interacting with the so called biological target you have to understand that molecules

with different functionalities is making interactions with the protein, which is could be receptor IN channel or inside or whatever. And these interactions are based on the features of the molecule that make light with oxygen or with nitrogen to make hydrophobic or bond interaction with the protein, with the amino structure of the biological target.

Q. Could we have a split screen with this and then the next page of the document?

Could I ask you to blow up that second paragraph?

Could I ask you to explain for the Court's benefit what is shown in this passage at the top of the screen?

A. Here it is mentioned in the more precise way that's an arrangement of the two chiral centers attached to the other cyclohexane ring considered is very important to keep the so called transconfiguration of hydroxyl group shown here in this picture and equatorial attachment.

Q. I see in that passage there's the word "cyclohexanol". Does that in any way relate to the structure within the ring C?

A. This is correct. Here cyclohexanol fragment is shown within the structure.

Q. Is the OH part of the ring C also a part of the considerations that Grunenthal was making at this time?

A. Based on the analyzes at this time of the available molecules, which were around 550, this hydroxyl group was considered as one of the crucial interaction points with the OC

receptor.

Q. Could we have the page ending in 46365. And could you focus on -- exactly.

Here you see four numbered items. Could you please explain for the Court what is depicted?

A. These are different categories of the pharmacological profile of the synthesized compounds. On one hand compounds without any opioid components are mentioned. Then compounds which have no opioid component and a weak opioid effect. And then the third category is a balanced ratio in terms of pharmacological activity of the opioid and non opioid components.

And the fourth category was considering relative opioid compounds where the opioid effect was the dominant one.

Q. How were compounds categorized amongst these four selections?

A. These compounds were categorized based on the pharmacological profile. At this time it was quite hard to understand if there is a structure guidance in these different categories if you have subsets of comparable compounds or different close analogs. We have found in all of these categories that it's really based on the pharmacological activity and not on the structural features.

Q. Now, and so would you have been able to determine which of these four categories a compound would fall into based

on the structure?

A. This would have been quite nice if they would have been possible. It was not possible.

Q. Now, could we have the page ending in 46358. And the top of the page.

Now at the time of this report, and just to make clear, was that retrospective report as of some date?

A. This was considered as a retrospective free report summarizing the chief manifest group was created in 1991.

Q. And did this report reflect any of your own work?

A. This was created in '91. I started my career at Grunenthal in '92.

Q. So it could not have reflected any of your work. Is that right?

A. This would not have been possible.

Q. Was Grunenthal optimistic at this time in 1991 about achieving all of the goals that had been set out in this report?

A. I think at least it was considered that it is a big challenge that the desired profile may be realized in one single molecule. This is what is written in the first sentence here.

Q. Could we have PTX 534T? And again you have a copy of this in your binder as well as the German language original?

A. Thank you. Okay.

Q. Now do you recognize this document?
A. Yes, I remember this document.
Q. What is it?
A. It is the meeting minutes of the project meeting we had in '94.
Q. Were reports such as this prepared in the normal course of business at Grunenthal?
A. This was normal procedure that any meeting was documented with meeting minutes reviewed by all participants.
Q. Do you recall anything particular about the background of this meeting?
A. Though it was a kind of crisis in '94 that with the work which was done so far, the desired features were obtained. And it was discussed what additional activity should be done for the future or even it was discussed to stop this project.
Q. If we could blow up the Professor Strassberger paragraph.
Could you see here a discussion of Dr. Strassberger's opinions?
A. Yes, I see it. I remember it very well.
Q. Who was or is Dr. Strassberger?
A. At this time he was head of computation and chemistry molecule and modeling at Grunenthal.
Q. And what did you understand Dr. Strassberger's opinions to be?

A. He is trying to summarize that as a features one molecule with a dual action good oral viability and pure enantiomer without being a metabolite is a goal which may have no real prospect of success based on the current data available at this time, analyzing the progress of the project.

Q. And we will look again at these four goals later but just bear them in mind and recall them.

Now, earlier we discussed Grunenthal's view that it was important to retain the trans cyclohexanol, the circle C of the structure that has now become common.

Do you recall that?

A. Correct. Yes.

Q. Did you synthesize compounds that had that cyclical background, backbone?

A. I synthesized compounds with cyclic backbone.

Q. Did you only synthesize those compounds?

A. No, I also tried to look to compounds with the linear carbon chain as a backbone.

Q. Did you inform your colleagues at Grunenthal about that decision to pursue that?

A. Of course I was informing my superior, which was Dr. Helmut Buschmann, head of this department, as well as Professor Winter who was at this point responsible for chemical research at Grunenthal.

Q. What was their reaction to your idea?

A. The reaction was not quite good saying if you open this molecule, you will end up with no activity because of the increasing flexibility. Or you may end up with molecules where it's too strong opioid activity correlated to the known open chain molecule slide Methadone and Fentanyl at this time known as strong energies and compounds which was not part of the desired profile that Grunenthal was looking for.

Q. But, you went ahead and made those compounds, correct?

A. So, I continued and to start to make this compound but also of course I continued making cyclic analog to convince my superiors.

Q. When you say to convince your superiors, what do you mean by that?

A. That they were saying you may lose in experiments but we can already tell you now what is the result of this experiment. It will not work, your hyperstasis.

Q. Could we have the demonstrative which I believe is Number 2 in the binders and Number 16 in Rob's deck.

Would you please explain for the Court what is shown on the screen?

A. Here is the first linear compound shown which was synthesized in my lab and it was given to pharmacological testing. And this compound was considered as the closest linear analog to the Tramadol chain because the linear chain has also ketones. And this was mimicking the C6 cyclohexane

ring of Tramadol.

Q. Could you show how it mimics the Tramadol structure?

A. Here it is shown the aromatic ring system, the hydroxyl functionality, as well as the nitrogen functionality. And the only difference of this molecule is that one bond was cleaved in the Tramadol molecule which was then giving this linear change.

Q. I believe you mentioned that you sent this molecule off to pharmacological testing.

Is that right?

A. This was sent first to a nuclear department and then afterward it was sent for pharmacological testing.

Q. What was determined about the physiological activity of this compound in those tests?

A. So, according to the screening cascade at this time at Grunenthal the writhing test was done. And it was considered, based on this testing, that there was only a low activity of this compound.

Q. Now, could we have PTX 330 on the screen?

Do you recognize this document?

A. Yes, this is the binder of my lab notebook or one of the binders of my lab notebook.

Q. Did you make and keep this notebook in the regular course of your work at Grunenthal?

A. Yes, of course.

Q. If we could just split screen with say the first couple of pages with this notebook.

Would you please explain for the Court what is shown here?

A. These are summaries as a kind of inventory of intended molecules to be synthesized in my lab.

Q. And how did you decide to make these particular modules?

A. So, it was an iterative process that first compounds which were tested and the pharmacological results were coming in to decide what is the next variation to test and to structure variations in terms of pharmacological differences.

Q. When you say "iterative process", can you expand a little more what you mean by that?

A. At this time it was a way to look for one structure variation and to check what is the consequence of the structural variation. And then to try to conclude what does it mean for the pharmacological activity. And it was done from molecule to molecule and comparing the incoming test results in terms of pharmacological activity.

Q. And Rob, if you could blow up that structure.

THE COURT: I'm sorry, what page is this in the exhibit?

MR. BEST: It's 14312 of exhibit, I believe, PTX 330.

THE COURT: I have that. And we've been looking at the upper right hand structure.

THE COURT: Thank you.

Q. Would you describe what structure is shown here?

A. This is the structure we have shown, we have seen in the slide before which was named as BN4.

Q. And that name BN4, can you explain what that meant?

A. There are different coding systems existing at this time at Grunenthal. And the code BN was, yeah, it was correlating to the lab where a compound was coming from. And it was indicating this was a compound which was sent to pharmacological testing.

Q. And whose lab did this come from?

A. BN is indicating that it was coming from my lab.

Q. And what does the four indicate?

A. Sorry.

Q. What does the numeral four indicate?

A. That's Number 4.

Q. And what significance did that have in your work?

A. So, it was the first compound which was synthesized and tested. And based on the incoming results, which were at this time quite disappointing, I was not in the situation to give up. And it was an ongoing process in designing and looking for new compounds.

So we followed, of course, the way to look for other

cyclic analogs. But, also I tried to put some more activities to understand why this first linear molecule was not showing the desired activity in the pharmacological testing.

Q. Now, could we have PTX 345 at Page 18944.

MR. BEST: And just a note for the record, there is a translated English translation version of this that we will be asking to enter into evidence but for purposes of today we only want to focus on the structures and the names?

THE COURT: That's fine.

Q. Could you blow up, Rob, the top of the page, please.

Now, looking at your binder PTX 345, is that a document with which you are familiar?

A. Yes, I am familiar with this document.

Q. And what is it?

A. This is one page of my lab journal showing the first time that Tapentadol hydrochloride was synthesized. It means, looking to the number, it's around 300 compounds later.

Q. When you say "300 compounds later", what do you mean?

A. That between the first results we have seen with BN4 indicating that B on 322 number, that more than 300 compounds were synthesized to come up with this molecule.

Q. And we have a name for that molecule today, right?

A. This is correct.

Q. What is that?

A. Tapentadol hydrochloride as shown here.

Q. What is the date on which you synthesized this?
A. It was the 26th of January in '94.
Q. And just to clarify, the date is written in the European fashion, right?
A. Yes, this is correct.
Q. Now, in addition to calling this BU 322, did you have any other nomenclature for this batch of Tapentadol hydrochloride?
A. There is also shown the so called lab code BU. It's related to my name and indicating the lab period was synthesized. The Number 322 is indicating it was the 322 compound which was synthesized in my lab.
So, following number is indicating to the method of preparation and the last number is indicating the batch. That means it was then molecule Number 322, 2 which the first method giving the first batch.
Q. And was there a batch number that you associated with this synthesis?
A. The batch number in the lab code was batch Number 1.
Q. Could we see PTX 326. Can we have that up?
Do you recognize this document?
A. Yes, I recognize it.
Q. What is it?
A. It's also one binder of my lab notebook collection.
Q. And could we have Page 1, Bates Number 13281 up? And

could I just focus on again the top?

Now, focusing on the code number, could you explain for the Court what that means?

A. This is BN 200. That means it was a compound 200 coming from my lab given for pharmacological testing.

Q. And what is the compound that is indicated as being BN 200?

A. This compound is now known as Tapentadol hydrochloride.

Q. And under the box marked charged, do you see that?

A. Yes.

Q. Again, we see the BU 322-1-1 nomenclature, right?

A. This is correct.

Q. There's also a zero there. What does that indicate?

A. So, it was a quite complex situation at this time at Grunenthal that the first batch which was synthesized and given for pharmacological testing was assigned as batch 0. So the first batch which was synthesized in my lab was considered as batch 0 for pharmacological testing. This is indicated in this box.

Q. Now, why did it require you to make 322 compounds in this series before you arrived at Tapentadol?

A. Because it was a quite long and intensive iterative step to learn from molecule to molecule, the influence of structured variations. And to see the effect on the pharmacological activity and to understand the complexity of

relevant features and structure variations which were having big influences on the pharmacological profile.

Q. Does that relate to that iterative process you were discussing?

A. Yes.

Q. Can we have up on the screen, Rob, what in your deck is slide 18 but I think is demonstrative Number 3?

Could you please explain for the Court what is shown here?

A. Here is the synthetic sequence shown which was used in the synthesis of the so called batch 0 which in fact was batch one in my lab.

Q. And does this page accurately summarize how you synthesized that batch 0 of Tapentadol?

A. Yes. We had started from the so called minimum phase of the pentanone, 3 Pentanone. And then the next step was introducing the aromatic ring system using a so called crin yet dixon (sic), which is an active reagent, to add to the carbon compound and as a consequence, because its molecule generated with two stereo centers, four possible stereoisomers were existing.

But here it was possible to have the so called chiral pair of diastereoisomer synthesized. However, there is no current information.

And as a consequence, this diastereomeric pair was

consisting of two enantiomers indicating BU 41 plus and BU 41 minus. And then a systemic resolution was to take place that was to put one isomer out of this racemic mixture. And then it was I tried to change this hydroxy group, the dextro hydroxy group attached to the aromatic ring system.

And it uses was a substitution reaction to change hydroxy group chlorine. And it was necessary to introduce chlorine for the next following step that it was reduced to hydrogen while not influencing the stereocenter.

So, the method of preparation that was chosen to keep the so called inversion of the stereochemistry during this methodology.

Q. And when you say to keep the stereochemistry, what do you mean by that?

A. To keep the absolute sense of the two chiral centers in terms of the attachment of the relevant substitutes.

Q. And they were kept -- were they retained? Is that the point?

A. Yes, retention is the correct term for having no change of absolute sense of the chiral center.

Q. And which stereochemistry was retained to the end of Tapentadol?

A. On one hand the so called arrangement of the two attachment chiral centers which was assigned as chiral and the chiral may exist in two enantiomers. And here only one

enantiomer the, so called minus enantiomer was depicted as the relevant molecule.

Q. And did you then only use the minus enantiomer for the remainder of the synthesis?

A. In this case having done the racemic resolution of the first synthetic passive, there is, two synthetic centers were generated. Only the minus enantiomers were used for the four ring steps.

Q. Once you had synthesized this compound, what did you do next with it?

A. Then it was the first step is to look for structured elucidation which is at this time available in particular methods. And after this was confirmed on my lab level, the compound was given to the so called analytic department which was an independent department checking the purity and structure of the compound.

Q. When you say an independent department, what do you mean by that?

A. So, it was handled outside the area of the synthetic chemistry. It was a different person who was responsible for the analytical department. And at this time it was quite important that this should be independent, that an independent check for incoming molecules was warranted.

Q. If we can, once again, can have PTX 326 on the screen. And focusing on page, you have it, again the structure here is

Tapentadol.

Is that right?

A. This is correct.

Q. How was this compound characterized by the analytical department?

A. This compound was characterized by in an aspect as a copy uses hydrogen and carbon nucleus. And then with IR and purity both were checked by synthetic chromatography.

Q. Could we have the next two pages on the screen split screened.

Could you please explain for the Court what is shown on these pages?

A. This is the analytical record of the so called purity test using thin layer chromatography on one hand and on the other hand also it's also showing the stability measured by thin layer chromatography in different arches in the 24 hours course to learn, to give a warranty under physiological test conditions in the department this compound remains this compound and is not degraded.

THE COURT: Which exhibit is this again number?

MR. BEST: This is exhibit, it's number PTX 326.

THE COURT: What's the page?

MR. BEST: It's Page 13282 and 83.

THE COURT: 13282 and 3?

MR. BEST: Yes.

THE COURT: Thanks.

Q. Now, if we could have the next two pages up on the split screen also.

THE COURT: I'm sorry, just going back to 13282, that was showing what? Your own purity analysis?

THE WITNESS: Purity by thin layer chromatography and stability if you have the compound dissolved and additional p h conditions in this compound remains the same after 24 hours kept in solution.

THE COURT: Thank you. So, purity and stability.

THE WITNESS: Exactly. Exactly.

THE COURT: Thank you.

Q. Can we have the next have 13282, I'm sorry, 284 and 85 on the split screen ?

Would you explain for the Court what is shown on these two pages which are the next two in the document?

A. Yes. So called H P and C chromatogram of BU41 is shown. So what we have shown in the synthetic ring that is 41 precursors and consisting here of two enantiomers. And here a so called chiral chromatography is used. That means the phase where you are testing the compound is chiral.

And having chiral compounds we have so called diastereomeric interactions which enables you to differentiate with the chiral column enantiomers. And this is exactly shown here that the resume is giving two peaks which is shown on the

left hand side and the material which was used during the synthetic pathway of 322.

Only one peak is shown. That means based on the test conditions it was considered as an enantiomeric pure compound. Enantiomeric pure means higher than 99 percent depending on the method of detection which was used.

THE COURT: Thank you.

Q. There is an indication at the top of the page, BU41, 1 plus 2 and BU41 numeral one.

What do those refer to?

A. This was a lab coding system at this time used in the department analyzing which chiral, H.P.N.C chiral compound. So the 1 and 2 was assigned to enantiomer one and enantiomer two. This is the meaning.

Q. Could we have Page 13286 on the screen?

Would you please explain for the Court what is shown here?

A. This is so called C.V. spectrum of the compound. So it was recorded giving light at different wavelengths to the molecule at what wavelengths the kind of absorption is taking place. And this is so called absorption curve known as the UV spectrum of compound which is quite normal analytical characteristic at this time.

Q. When you say it's a spectrum, could you explain how that relates to the compound? Withdrawn.

That's a little inartful. Let me ask this, would you characterize the spectrum as being like a fingerprint of that compound?

A. You can assign any spectroscopic compound as a kind of fingerprint but it doesn't tell you what finger you are looking to. So, it's only the compilation of different analytical which make sure you use the confirmation.

This is one that shows that UV absorption based on the function groups present in the molecule. That's the meaning which is shown here, is the absorption band is indicating that you have an aromatic ring system within the molecule structure. This is what an expert could extract from this curve.

Q. And what you extracted from the curve. Is that right?

A. It was a confirmation that the aromatic ring system was confirmed with this UV spectrum.

Q. Can we see the next page, please. Can you explain what is shown here?

A. This is so called infrared spectrum. That means it was, it is still a normal technique to characterize compounds with the so called IR method where also different radiation, different wavelengths are given to this compound. And it's also indicating related to the wavelengths.

Wave number, that means the wavelengths, the specific interaction with irritation and a molecule is taking place. Given the signals and specific signals you can correlate to

specific structure features. Again here the aromatic ring system could be detected and as well as the hydroxy, the absence of the hydroxy group which would have a different signal if it would have been present.

Q. Can we have the next two pages on the split screen? Would you please explain what is shown here?

A. This is another spectroscopic method known as hydrogen NMR method where on one hand you are looking to the resonance spectra of the hydrogen present in your molecule. And with this technique, you can see on one hand how this hydrogen attached around the molecule.

Q. And could we see the next two pages as well? Could you explain what's here?

A. Here is a complete so called hydrogen NMR spectrum shown with the alignment of the different frequencies and the so called shift. That means at what wavelengths the absorption is taking place.

Q. And these are on pages 13291 and 92, correct?

A. Correct.

Q. Can we have the next two pages, 13293 and 94?

A. This is the representative so called carbon NMR spectrum on one hand with the signals indicating, showing the single carbon atoms present in this molecule. And the second page is showing the environment of the carbon extract. That means you have 2 or 1, 2, 3 or 4 substitutes. You can

differentiate with the different direction of the peaks in the second page.

So, overall it's, with all other spectrum, a confirmation that you have the correct number of ketones which have the correct substitution pattern.

Q. And all of these analytical data we've been looking at for the last several pages, do they relate to a batch 0 Tapentadol?

A. This is indicating batch 0 also indicated as BU 322/1/1.

Q. Now, could we have DTX 1183 up, please? And again could you just blow up the top ?

Would you once again focus in on the batch? Would you please explain what is shown here?

A. So, here it's indicated it was the first batch which was resynthesized after the primary testing in the Department of Pharmacology. And it's, the second BU code is indicating that another method was used to generate this batch one.

Q. So, this was a resynthesis of your first batch of Tapentadol. Is that right?

A. This is correct because larger amounts were needed. So it was resynthesized with further pharmacological testing.

Q. And this has been called, in the course of these proceedings, batch one, right?

A. Yes. In fact, batch two -- the lab bought batch one

for testing in the pharmacological department.

THE COURT: Could we just say that one more time? This is showing batch one but created again.

THE WITNESS: It is batch one. This was, this is the first resynthesized batch which was given for pharmacological testing but it was the first batch resynthesized. It means it's the second batch because the first batch was assigned as batch 0. It's a little bit confusing.

THE COURT: The other one is assigned as batch 0? This one is assigned as batch one?

THE WITNESS: Exactly. And this means it's the second existing batch but assigned as batch one. That's the most logical way to assign batches.

THE COURT: I understand.

A. Unfortunately done at this time at Grunenthal.

THE COURT: So, this one we are going to refer to as batch one?

THE WITNESS: Yeah.

THE COURT: Very well. And the date on this one is evident?

THE WITNESS: Is April '94.

THE COURT: '94.

THE WITNESS: Was some weeks later after the first synthesis.

THE COURT: I understand. Thank you.

Q. Could we have the next demonstrative which is number 3 in your book. And Rob, it's Number 8 in your book. No, sorry, I it's 32, maybe.

Could you explain for the Court what is shown here?

A. Here is synthetic sequence shown which was used to synthesize the so called batch one for pharmacological testing. In principle all transformational steps are the same. But, we have changed the order of the sequence in the last steps because we were asked to synthesize larger amounts. That means more than one gram.

And with the lab equipment available at this time, it was quite difficult to synthesize micrograms of batches. And so we were looking to investigate a more optimized procedure. And what was changed here in this sequence in comparison to the batch 0 was the so called reduction of the chiral ring which was introduced in the methods we were using. And then the relevant reduction step was taking place.

And this reduction we were using same bolo (sic) hydrate at this time which is a quite complex reagent. You have to prepare in vitro, insolvent test is in vitro. And so the ability of reagent is quite low.

And as a consequence large amounts of solvents were necessary to have sufficient concentration of this reagent available. This reagent was quite sensitive in the first

synthetic pathway. We have used hydroxy compound for the reduction and the hydroxy compound present in the aromatic ring system was demanding that one one cyclometric service of this reagent was used to make the salt of this hydroxy compound.

So, it means we would need it twice as possible simple hydrate concentration which was limiting the size of the flask that we had at this time.

So we decided first to make the reduction using the methoxy group. That means we were able to have only one cyclo metric ratio of reducing reagent available. This was allowing us to do the same size of flask with higher concentrations and this was the sense. So it means in principle, the sequence is exactly the same.

So the order of transformation first changed to have larger amounts available with the same synthetic pathway.

THE COURT: Would it have changed the substance at some point?

THE WITNESS: Not at all. It was just a matter, the substances is exactly the same. It was the order that the transformation was taking place. So we have used hydroxy chloride compound as a conduit against larger amounts of this reducing reagent that was used.

And the second way we have kept the methoxyl group that means only half of the reagent was necessary which allowed us to have larger amounts of the same. So that means the

sequence and the transformation steps were exactly the same, only the order was changed in the last step to save volume and to make larger amounts.

THE COURT: Thank you.

Q. Rob, can we have PTX 345 up again at Page 18952 and just focus at the top again.

Dr. Buschmann, can you explain what is shown on this page?

A. This is indicating here the second, the last step of the so called synthetic pathway. Number 1 is indicated in 322/2. And here it's shown the final step, that means the methoxyl is the cleavage of aromatic oxy group which is hydrobromic acid on the reflux conditions.

Q. And again does this synthesis relate to batch one?

A. This synthesis is related to batch one for pharmacological testing. And it was the first batch using in this method which is indicated as slash one in the BU code system.

Q. Can we have DTX 1183 once more? And in specific, well first off, could I ask you whether you recognize this document?

A. Yes, I recognize this document.

Q. What is it?

A. It's so called certificate of analyzers which was prepared for this first resynthesized batch, batch Number 1, giving the identity and purity as later in the department of

analytical chemistry.

Q. What was the date of this document?

A. This is the 21st of April, 94.

Q. Now, focusing on could you explain for the Court how this analytical department treated this sample?

A. Yeah. Based on the analytical assessment we have seen for the batch 0, not all the spectroscopic analyzers were repeated for the batch because it was only controlled, the purity, based on thin layer chromatography which was confirmed in the batch 0.

Then the so called stereochemical purity based on the chemical, stereochemical purity based on precursors was rechecked and the identity was checked by hydrogen NMR which was then as a kind of fingerprint warranty that it was the same structure which was resynthesized.

Q. Did you perform this characterization yourself?

A. This was done by the experts of the analytical department.

Q. What is shown on the next page? I'm sorry, actually could we turn to Page 86895?

Could I ask you to describe for the Court what is shown here?

A. Here is exactly shown the hydrogen NMR where the certificate of analyzers was referring to, indicating its molecule BN 200 with assignment minus enantiomer as additional

information and indicating batch one, which was the first resynthesized batch for pharmacological testing.

Q. So, once you had synthesized and had this compound characterized, what did you do with it next at Grunenthal?

A. So, once we handed over this compound to analytical department, this assessment was done. And then analytical department was transferring the vial, including the compound certified with purity and identity to the pharmacological testing which was a different building, a different department. And compound handling was then independently from the chemical labs handling in the pharmacological department.

Q. What was your understand of what they did with it?

A. At this time a so called screening cascade was established. So, based on the pharmacological profile Grunenthal was looking for, it was quite, even at this time, quite unusual to use as a first test model and in vivo test model because every company at this time were first checking the in vitro profile.

But Grunenthal decided that we were looking for analgesic activity because they used a so called writhing test model PO which allows you to have a lot of information available during only one experiment.

First of all, you see the availability of the activity. And the writhing test is a standard test model for testing analgesic compounds. And if it's seen effect, you know already

it's available and you have an analgesic effect.

And based on this, it was then decided if this compound was of interest to elucidate the receptor profile looking through the mechanisms of action which are responsible for this observed activity. And at this time all companies were focusing first in vitro and then to go back to in vivo testing.

And in the latest 19, 2015 because of generating only in vitro data, a lot of companies may go back to first test a single dedicated compound in vivo. Because we have one experiment, much more information. And this was exactly done at this time at Grunenthal.

THE COURT: Did you test it on rats or anything else?

THE WITNESS: This was based on the amount of available mice were used because lower amounts were necessary for mice testing.

THE COURT: So the first testing you did in vivo was on mice?

THE WITNESS: Was mice.

Q. You used the term PO. Could you explain what you mean?

A. This is the term per os which means oral application.

Q. Were you the one who performed these writhing assay experiments?

A. No.

Q. Who did them?

A. They were done by the experts at the pharmacological department.

Q. Who is the head of that department?

A. At this time head of this department was Dr. Fitlas (ph).

Q. And what was his first name?

A. Helmut Fitlas.

Q. Now, could we look at PTX 1602 at tab M as in Mike? We are looking for the Bates number that ends in 8124.

THE COURT: It's 8124?

Q. 8124, yes. Now, Dr. Buschmann, have you seen this document before?

A. Yes, I have seen this document before.

Q. What is it?

A. It was generated by the Department of Pharmacology to report test results. In this case the writhing test. And here it was seen that one dosage, it was the standard dosage used, 21.5 mix per KG.

Q. Which compound was tested in this experiment?

A. This is the test result from the compound BN 200.

Q. Also known as Tapentadol?

A. Now known as Tapentadol hydrochloride.

Q. Which batch was this?

A. This data are coming from the batch 0 which is indicated in the upper part of the document. And it was the

first test. So it was logical that the batch 0 was tested is the first model. And this is the first test results coming in for this compound.

Q. When were these results obtained?

A. These results were then obtained in February 18th of February '94 as indicated in this form page.

Q. Now, could we look at Page 8129 GRTNUC8129.

Are you familiar with this document as well?

A. Yes, this is additional information of the same experiment where the time points of analgesic energy in this terms reduction of pain, according to the time points of measurement are recorded.

This is exactly the same experiment which we have seen before, only with additional information referring to the measured time points.

Q. When were these data obtained?

A. This is indicated from 28th of February, '94.

Q. Could we turn back to the page ending in 8123?

Would you please explain for the Court what is shown here?

A. So, as the first test model, the first dose was chosen and this first dose was the 21.5 mix kpg. But, with the first dose some analgesic activity was observed, then different dosages were used. And this is a quite normal process to look for the so called ED 50 value.

That means what amount you have to give to the animal where you could achieve 550 percent activity. So there is a kind of quantification based on different dosages given to the animals.

Q. When were these results obtained?

A. These results were then obtained after the first standard dose was tested. And here it's indicated the fifteenth of March '94.

Q. Could we have 8135 up?

Would you please explain what is shown here?

A. Here the same analgesic test model was used. But here the results of different dosages are shown. But using a so called another application would not pair us here. It's I.P., intraperitoneal.

Q. Is that an injection?

A. It's a kind of injection but it's not the apparent injection. It's the injection going below the skin.

Q. When were these data obtained?

A. This data were obtained also in March '94. And this report is dated on the 16th of March, '94.

Q. And one last one. Could you look at 8125?

Could you briefly explain what is shown here?

A. This is again the same test model using another application route. In this case it used I.V., intravenously. That means giving directly to the system. And this I.V. test

was normally used to investigate what is the so called oral viability and without having the mechanisms.

Once the compound is given orally, what happens is this compound is absorbed in the stomach and then transferred to the blood system either directly to the blood system. And as a consequence you tend to get the effect of the compound. And if not, this is necessary, this was the meaning of intravenously testing.

Q. When was this data obtained?

A. This data was also done in March here. This sheet has indicated it was the 13th of March, '94.

Q. Now, considering these animal data for Tapentadol we have just reviewed, could you please summarize what you felt that you learned from these experiments?

A. So, first of all, following the first streaming experiment giving a standard dosage, analgesic energy of this compound was found. Then different dosages were given to estimate and to quantify the so called ED 50 value. And different application roots were tested and showing that there is a high activity of this compound giving it intravenously. But, also sufficient activity giving it with a PO route. This was a conclusion out of the sheets we have seen before.

Q. And why was it important to have information about obtaining the PO route?

A. Because at this time Grunenthal was looking for

compounds with oral activity for the intended pain sequence. So any I.V. application was not considered as a desired profile application.

So, this was the why the writhing PO test was the first animal model to look for oral activity.

THE COURT: I'm sorry, just to clarify, the PO test is orally administered?

THE WITNESS: Yes.

THE COURT: What does PO stand for?

THE WITNESS: Per os.

THE COURT: Thank you.

Q. Now, could I have document DTX 1144T?

Dr. Buschmann, are you familiar with this document?

A. This document is a so called project analyzer report which was introduced as a new steering pool at this time at Grunenthal.

Q. Were records such as this kept in the normal course of business at Grunenthal?

A. From this time onwards these project analyzer reports were performed two times a year for any project active at this time at Grunenthal.

Q. Could we have page, what has been marked -- it has multiple markings. But, I'm going to refer to it as GRTNUC 66993.

And focusing on the heading labeled Current state of

the project. Do you see that?

A. Yes, I see it.

Q. Could you summarize for the Court what the current state was as of this date?

A. This is again showing the four categories we have seen in the '91 report. And here it's stated that in the meantime more than 800 compounds were tested in vitro. Forty in one of the four categories as strong opioid or dominant opioid with a weak non opioid component, opioid and non opioid component in the balanced ratio and a non dominant, non opioid mechanism of action.

Q. And had all of these 800 substances been produced in your lab?

A. No, also a second lab was active at this time. But, during the course, I was and later on responsible as head of the second lab. But, we were using for the second lab another coding system. So it's yes and no is the answer.

Q. And were all of these compounds the linear compounds that you discussed previously?

A. Not at all. It was complete compound collection tested in this project, and the majority of them were cyclic compounds.

Q. Including the 550 that we had discussed in the 1991 group?

A. Exactly as seen before.

Q. Now, could we focus on the final paragraphs on this page?

You see there's a discussion of Stage 2. Could you explain for the Court what Stage 2 I guess with a reference to Stage 1 of this project meant?

A. So the Stage 2, that's the most interesting category of compounds where compounds having an opioid component with a second mechanism of action which is here specified as the so called nuederine optic inefficient effect. And both mechanisms of action together should have or should be responsible for the overall pharmacological activity.

So, based on what we have seen before, these are compounds which are falling into so called categories three where you have a balanced ratio between opioid components and non opioid components. And more precisely the nuiterine (sic) component as the non opioid components.

Q. You see there's a discussion of how this is a true innovation.

Can you explain what that meant?

A. Based on all the things we have seen before, it was considered that it may not be possible to have both activities in one molecule with an enantiomer without being a product available. And so here it is a statement that it was an achievement to get some of these molecules. And these molecules were considered as a true innovation base after all

these drawbacks we have seen before in this project.

Q. Could I have the Page 67031?

So, at this point later in the document you see this risk assessment?

A. This is correct.

Q. Can you explain what is meant by this?

A. So, also the relevant project people were asked what are the risks. On one end you were referring to the achievements having found the molecule, these two mechanisms of actions. But here also the risk was analyzed that double activity may result also in an increased side effect profile.

And this is exactly what's mentioned here. With the benefit of having two mechanisms of action, you have also the risk that these two mechanisms of action are computing to undesired side effects.

Q. And were you able to predict the magnitude of those risks on the basis of the structure of the compound?

A. No. This is not possible because this is a broad investigation with a broad animal testing in different side effects related to cardiovascular side effects seen as side effects and other things.

So this is a summary statement of a huge compilation of additional data coming from different animal experiments.

Q. Could we see the page that's marked 67008 and the chart?

Actually going back to the page, do you see at the top there's this notation competing substances and development?

A. Exactly.

Q. To what did that refer?

A. So this was one part of the exercise for the project analyzers to give an overview what companies in the pain field were working on what type of projects.

Q. And now looking at the chart, could you summarize what is shown here?

A. Here are at this time identified activities in the industry for summarized that they were companies identified working on the so called sub selectivity of the opioid receptors known as copper and delta one. They were compounds working on peptide compounds, neuropeptides, nasal inhibitors and also compounds which were coming from the so called alpha 2 adrenergic agonist. And this was mainly referring to the analgesic activity of Grunenthal at this time.

And the strong opioids known as Fentanyl MU analog which was also considered here as well, the so called partial opioid agonist compound.

And at this time revealing the activity and function the copper opioid receptors. Also compounds were identified showing the strong analgesic activity were not pure agonistic morphium which is a gold standard of the MU agonist here other compounds which are more complex structure.

Here other compounds which have that structure like morphine were considered as analogs whereas functionality was considered as an advantage to overcome the typical opioid side effects and to look for a mixture of partial opioid agonist or antagonist functionalities.

Q. And did any of these competing substances enter the development of the drug Tramadol?

A. At this time no other activity using Tramadol and the pharmacological properties of Tramadol were identified where other companies were active.

Q. Only Grunenthal?

A. To our best knowledge at this time it was not possible to have any other companies seen active here.

Q. Could you put the next 2 pages up which are 67009 and 10 on the split screen? And just focusing on the column headers, the first column rather.

A. These are more detailed information coming from the list on the previous page where additional information were summarized for the categories we have seen before.

Q. And paging through these tables on these 2 or 3 pages in your document, were any of the companies that are indicated working on Tramadol other than Grunenthal?

A. This is again a confirmation that with these activities, no activity in these different treatments were observed relating to working on Tramadol.

Q. Now, about how many different compounds did you synthesize over the course of your work in the Tramadol successor project?

A. I have to recollect. I was working January 2002 and I was working on around 800 compounds. 812 was the last number in my lab I think.

Q. Did there come a time during your work at Grunenthal that Grunenthal decided to file a patent application on the basis of this work?

A. This is correct.

Q. Could we have split screen of PTX 303 and PTX 306?

THE COURT: Going back to the 812 compounds, was this before this compound or was it in the entirety of your --

THE WITNESS: This was overall compounds I have synthesized during my time at Grunenthal.

THE COURT: Thank you. Do you know how many it was before this one, the last one we're looking at?

THE WITNESS: I think in the course it was around 900 compounds which were considered as analogs of the Tramadol successor project.

THE COURT: Nine hundred compounds?

THE WITNESS: Around 900, below 1,000, was 970, something like this.

THE COURT: All right. Thank you.

Q. Now, we have up here PTX 303 and 306.

Are you familiar with these documents?

A. Yes, I'm familiar.

Q. And what is the document on the left?

A. This is a declaration and certification of the German patent, that application.

Q. And is the document on the right the English translation of that?

A. This is correct.

Q. So, for purposes of the screen, we will be referring to the English version.

A. Yes.

Q. But obviously you have both in your book to the extent you would like them.

A. Yes.

Q. Could we have the page that's marked GRTNUC 18953? And, I'm sorry, this is in PTX 345. And could we split screen this with PTX 306 which we had up just a moment ago?

On the left I believe we discussed earlier this is batch one of Tapentadol hydrochloride that had been synthesized in your lab. Is that right?

A. This is right.

Q. And is that synthesis reflected anywhere in the document on the right, PTX 306?

A. This was in fact the synthetic sequence which was documented in this application.

Q. And could we see example 25 of this document on the right?

THE COURT: I'm sorry, what is the second part of the split screen, Page 34? What's that coming from?

MR. BEST: On the right that's Page 34 of PTX 306 the English translation of the German patent application.

And Rob for example 25 could we have the whole example down to.

Q. Now, looking at example 25 of PTX 306 and comparing it with your notebook Page 18953, are the structures depicted in both of these documents identical?

A. The structures in both documents are identical.

Q. And is the chemical name that's depicted in both documents identical?

A. The chemical name is as well identical in both documents.

Q. And is the melting point identical?

A. No, the melting point is not identical.

Q. Do you know why that?

A. My best guess it appears a typo which was not detected in the further prosecution.

Q. Focusing again on the chemical name underneath the structure of either one, since you identified them as being identical, is this the correct chemical name for the structure depicted there?

A. This is the correct chemical name, however, the chemical descriptors indicated as 1S 2S are not correct.

Q. Now, in 1994 when this application was filed, were you knowledgeable about stereochemistry?

A. Yes, there was stereochemical knowledge available.

Q. Did you know the uses for the R S nomenclature to compound?

A. I used the so called descriptor was well-known, yes.

Q. Do you know how the descriptors here were incorrect, as you put it?

A. Here the 1S 2S configuration is shown and in fact a structure which is shown above which is symbolizing --

MR. PATEL: Hydrochloride. It should have been indicated as 1R 2R.

Q. Did you help prepare a demonstrative to help explain for the Court how this mistake arose?

A. Yes.

Q. Could we, Rob, have I think it's slide Number 5 for everyone's book but 44 in your book?

MR. BEST: May the witness approach the screen? It may be easier.

THE COURT: Absolutely. This is demonstrative?

MR. BEST: It should slide five in the notebook.

THE COURT: You may approach the screen. I go from low numbers to 16. Does that make sense? I go from 2 to

16. What number is this, 44?

MR. BEST: So --

THE COURT: I have it.

Q. So Dr. Buschmann, please approach the screen and explain what you meant by how this mistake arose.

A. Here the stereochemical drawing is shown which is indicating absolute sense of stereochemistry indicated of the precursor S. And S is not changing during the transformation steps. That means the way it houses substituents are attached to this current center are exactly the same.

And the most logical way was in my thinking that this absolute, since if this is not changing, the descriptors S S should also be equivocal for the final product. Because the absolute sense doesn't change. This was the basis of the most logical thinking looking to the structures.

However, the descriptors can't get rid of the indicating chiral center SS and RR so called artificial descriptors which are based on different priority rules. But, they are not reflecting the absolute sense of the chiral center. And this was the basis of this error that nothing was changed losing the absolute sense from the starting material to the final product. So the S S configuration was considered also S S configuration --

Q. What is the structure on the left?

A. The structure on the left is starting with period

indicated S BU 41 minus where the absolute stereochemistry was confirmed by different methods. We used the chiral HBC method before.

Q. How did you know then that the structure on the right was the expected structure of the compound you were making based on that starting material?

A. Because the new steps, the method of preparation, knowing that so called stereochemical retention is obtained, then the sense going from here to here should exactly reside in the same attachment of the substitute shown in the final product given the minus 21.

Q. Thank you, Dr. Buschmann.

THE COURT: With respect to the 1S and the 2S, we were just looking at the patent which should have been --

Q. PTX 306?

THE COURT: Which should have been 1R and 2R. What was it in the lab notebook?

THE WITNESS: This lab notebook is 1S 2S because it was not detected, this error.

THE COURT: It was not detected?

THE WITNESS: Yes. And it should have been.

THE COURT: And it should have been 1R, 2R?

THE WITNESS: Yes.

THE COURT: Why was the error actually in the lab notebook? Do you know? Was it and error in the lab notebook

as well?

THE WITNESS: Yes, because it was copied from the lab notebook. The lab notebook, it was assumed, not changing the stereochemistry, that the product would also have SS. This was the way of thinking at this time which was, of course, with the application of this root, not correct.

THE COURT: Not correct. All right.

Q. Now, would you please put up PTX 6668.

Dr. Buschmann, are you familiar with this document?

A. This is a U.S. patent application.

THE COURT: In terms of the lab notebook, was the melting point correct from the patent to the lab notebook?

THE WITNESS: No, this was not correctly transferred to the description of the patent example. This was also not detected and I can't consider what was available. It was not detected so I can say it was just a typo.

THE COURT: Just a typo.

THE WITNESS: Unfortunately a typo.

THE COURT: So, is the typo on this structure in terms of 1S, 2S, it should have been 1R, 2R and the melting point as well?

THE WITNESS: Yeah, the melting point is a typo and the assignment of 1S, 2S was an error. But, based on the assumption that is the absolute sense of stereo chiral, it was not changing.

Q. When you say "not changing", not changing from what?
A. Not changing in the absolute sense of the attachment of relevant substituents around the chiral center.
Q. And from the chiral center of what?
A. Of the two chiral centers of the Tapentadol hydrochloride molecule.
Q. And starting, so going from a starting material to Tapentadol hydrochloride, the stereocenters were not changing their absolute configurations? Is that what you are saying?
A. This is exactly what I wanted to say. The absolute sense was not changing but the artificial descriptors were changing. And this was not detected or considered.
Q. How did you know that the absolute configuration was not changing between the starting material and Tapentadol?
A. Because of the confirmed stereo chemical structure of the starting material and the method of preparation of the used steps and the reagent which were used for the transformation steps.
Q. Thank you.
THE COURT: Thank you.
Q. Now, this document which has been marked PTX 668 and which you identified as the U.S. patent and this is I think for the rest of your proceedings will be referred to as the '737 patent.
A. Yes.

Q. You're listed as an inventor of this, right?
A. That is correct.
Q. And there's a fellow named Wolfgang Strassburger listed as the same Professor Strassburger we heard about earlier?
A. Yes, head of computation modeling department at this time at Grunenthal.
Q. And Elmar Friderichs is the same Elmar Friderichs you discussed earlier?
A. This is correct.
Q. If I can ask, Rob, to split screen this with PTX 306 and in both instances look at example 25.
Once again, for purposes of 306, this is page, I believe, Bates LGRTNUC 9333. And then for PTX 668 it's JN_Nucynta_0058138.
Now, comparing example 25 of the translated German application on the left with example 25 of the '737 patent on the right, once again, are the structures depicted here identical to each other?
A. The structures depicted here are identical.
Q. And was the synthetic methodology to reach this compound identical in these two documents?
A. Yes.
Q. Are the names of these two compounds underneath the structures identical?
A. The names are not identical because here is the

correction of the first area center where the hydroxy group was exchanged by hydrogen was corrected to R, 1R.

Q. And did you help prepare this demonstrative to explain why the second stereo center was not correct in this instance?

A. Yes, because it was considered that the absolute sense was not changing. It was just in the first area center the change of R, from S to R because oxygen was replaced by hydrogen. And since in the second chiral center no transformation was taking place, it was considered that should also not be a change of the chemical descriptor.

However, this was also an error because the change of the first chiral center following subset rules of the conventional analog nomenclature system that alters the change of priority of the second chiral center. Indeed nothing was changed. But, as a consequence the descriptor 2S is not the correct one as indicated in the name.

Q. When you say the second stereo center was unchanged, could you point out with your pointer or perhaps you can approach the screen to show that?

A. Because here the second center is exactly the same because no transformation, nothing was changed during the transformation steps. So what starts here starting at hydrogen here going to hydroxy here going to hydrogen here, the sense was the same.

But using different priorities to make the attached

atom the air descriptor was going from S to R and here no transformation was taking place from the sequence we had seen before. And it was considered that it should have been the same configuration. But, having the change of this stereo chemical descriptor here, it has the consequence in the priority name, the stereo chemical descriptor which was not detected in the first step.

Q. Could we have what I think in your deck, Rob, is 47 and I think in everyone else it's six.

When you say that the second stereo center was unchanged?

A. As you see here from the starting material to the final product here, the change of hydroxy against hydrogens was taking place and of course the substitution of the hydroxy group here. But it wasn't the chiral center and the second center which is assigned here as S, no chemical transformation was taking place. It was exactly the same because no transformation, no chemical reaction was taking place at the center.

And as a consequence it was considered that this center should remain the same. And it was not detected at the influence of changing the first chiral center as influenced the priority roots of the artificial conangle relux center, the second.

Q. When you say conangle relux system what is that a

system for?

A. This is cell system introduced in chemistry to differentiate the chiral centers, chiral atoms with R and S.

Q. And?

A. Differentiate.

Q. Is that a convention?

A. I would consider this to be a convention of chiral center of central chirality? Maybe I have to add there are other several nomenclature systems depending on the nature of chirality even existing today. So R and S is assignment of one chiral center. But, you have also chiral elements which are not center chirality.

And so you have a lot of different nomenclature systems still today available. And depending also on the number of chiral centers within one molecule, you are also applying different descriptors which we have done also assigning the attached two chiral centers with three enantiomers, for example.

Q. Do these different names effect what the actual structure is that you are trying to describe?

A. Not at all. They are descriptors trying to bring, invert what is shown in the structure shown above. So, the relevance is the chemical structure that this chemist was looking to. And there was a reason that the chemist was looking to the structure and not this descriptor, considering

all relevant information is shown in the chemical structure.

Q. And the chemical structure that is in example 25 was the identical structure to what was in your notebook for batch one?

A. Exactly.

Q. And for batch 0?

A. Exactly. It was the same. Now, in addition, also another element indicating the sense of chirality is included in the name. And this is a minus. That means optical rotation direction which is an independent physical method to differentiate two enantiomers. Based on the chemical structure and based on the optic rotation direction, there was no doubt that it was the wrong name. And this was the basis why it was not detected by me or by my --

Q. Could we have PTX312.

Are you familiar with this document, Dr. Buschmann?

A. Yes, this is reissued version of the patent application.

Q. And I think in our proceedings we are calling this the '593 patent. Will you understand me to mean this document if I use that terminology?

A. Yes, I do.

Q. And are you listed as an inventor on this document as well?

A. Yes, I am.

Q. And are the other two inventors of this patent the same as the prior application?

A. Yes Strassburger.

Q. Now, if we look at example 25 of this document.

THE COURT: Would this be a good time to break just for the Court reporter for a few minutes?

Q. Actually it would be just fine.

THE COURT: Would it be okay? Thank you so much. We are going to come back in about five minutes time and move on with the testimony. Thank you so much.

You are excused, sir. Thank you.

(Whereupon a short recess was taken.)

THE COURT: Let's resume with the witness. You may come forward. Thank you.

Q. Now, Dr. Buschmann, welcome back.

A. Welcome.

Q. In the course of obtaining the '737 patent regarding your work at Grunenthal, did you submit a declaration to the U.S. patent office?

A. This is correct.

Q. We have PTX 390. Are you familiar with this document?

A. Yes I am.

Q. Is this the declaration that you submitted to the PTO?

A. This is correct.

Q. And if I could ask you to look at the chart toward the

end of this document, first off, could I ask you to explain for the Court what you're attempting to show in this chart?

THE COURT: What page is that? GRT NUC22110?

MR. BEST: It's on --

THE COURT: I have it.

A. The main intention was to demonstrate influence of the relative stereochemistry. Because having two chiral centers attached to either forced stereoisomers are possible. And that mean two pairs of diastereomeric molecules are existing.

And here the relative configuration differences of the threo enantiomer in comparison to the R so the enantiomer is compared in terms of the overriding test. This is indicated in the table.

Q. Could you split screen this with I believe it's 22112?

So, you see there a notation ED50 writhing?

A. This is correct.

Q. Could you explain what that means?

A. This is a dose dependency trying to quantify an analgesic activity in terms of ED 50 value. That means how much amount is needed giving to the animals to achieve 50 percent of the analgesic effect.

Q. And there was also a column labeled percent inhibition. Do you see that?

A. Yes.

Q. Could you explain what that means?

A. So, this is the readout of the animal experiment giving one dosage. If you have one dosage, you can only estimate what percent inhibition of the maximal effect is detected and the ED 50 is related to different dosages.

Q. Now, why are there not -- well, withdrawn.

You see that there are not percent inhibition data for all of the compounds in this table?

A. Yes.

Q. Why are there not data for all of the compounds?

A. Because once you were able to estimate ED 50 value, then this is data point which has much more value because it is showing the activity at different dosage forms and not only the percent inhibition at one dosage.

Q. And looking at the last row of this table, would you please explain what is shown here?

A. Here is the influence of the relative stereochemistry of the diastereomer isomer enantiomer, diastereomer of Tapentadol shown with also the writhing test data in terms of ED 50 is given?

Q. And what is disclosed with regard to Tapentadol?

A. So, it is also showing that the activity measured in this animal model is also detectable with a diastereomer of Tapentadol.

Q. Which of these structures is Tapentadol?

A. The left one indicated as example 25 and indicated with

the compound number minus 21.

Q. And what was the ED data for that compound?

A. Here it is given 31.3 mixed kg.

Q. Following your synthesis of hydrochloride and the other linear molecules we discussed earlier, and following the analytical chemistry and the physiological testing such as this, what did Grunenthal do next with the molecules?

A. So, they were looking for other pain models using different species and then starting out to investigate the side effects in terms of cardiovascular safety and seen as safety and also to investigate the pharmokinetics profile of the compound.

Q. Could we have PTX 544 up?

Are you familiar with this document?

A. Yes.

Q. What is it?

A. It's also one part Tramadol analog showing the slides prepared in the meeting of the project team.

Q. And if we can put up page GRTNUC 71995 and just focusing on the structures.

Would you explain for the Court what was shown here?

A. These are different structures which were investigated in depth with much more animal, pain animal testing, as well as investigating potential side effects of this molecule. So they were considered as interesting compounds to be investigated in

more detail in terms of activity, efficacy and side effects.

Q. And what was the date of this report?

A. This was also in October '94. It is indicated here the 27th of October '94.

Q. So, at this time how many of these compounds had been synthesized by you or in your lab?

A. Six out of there because I was also head in the meantime of another lab indicating the EM coding system where I have continued the old lab code. And the only compounds which were not synthesized under my supervision were in zed compounds in zed 57 and 69.

Q. You are saying in zed 57 as in Z in American English?

A. Sorry, this was wrong spelling, yes, in z-e-d.

Q. Of these six compounds that were excluded, Z59 and Z67, were all of these linear compounds?

A. Also cyclic elevators are shown here.

Q. Did this selection of compounds that were being carried forward at this time remain constant through further development at Grunenthal?

A. Yes. So, it was investigated and that was a lot of incoming data and these compounds were continuously characterized.

Q. And did you carry forward the analysis of all of these compounds in particular going forward or did they change over time?

A. It was depending on what information was necessary to come to a comparison or decision.

Q. Now, I believe you mentioned various characteristics like bioavailability, toxicity and so forth.

Did you attempt to rank the characteristics of these compounds on the basis of those characteristics?

A. This was done as an exercise to make a kind of prioritization to taking into consideration all different aspects of the compound profile in terms of efficacy, in terms of safety, in terms of all chemical properties, for example.

Q. Were you able to do those rankings based on the structures of the compound?

A. No. This was and it is still not possible to do that. I have this multiple information coming from in vitro, in vivo and other data which may be correlated to one structure feature. Impossible.

Q. Is one of these compounds Tapentadol?

A. Yes, indicated here as being 200 minus.

Q. Now, could we see the document that's been marked PTX 537?

Are you familiar with this document, Dr. Buschmann?

A. Yes, I'm familiar with this document.

Q. And what is the date of it?

A. The 22nd of February in 1995.

Q. And this document appears to be an English translation

marked GRTNUC 67991_T et seq.

Could I ask to see Page 67193?

You see here three tables, correct?

A. This is correct.

Q. Does this relate to the ranking process that you discussed earlier?

A. Exactly. These are different categories of ranking which are here and summarized in these tables.

Q. And what was shown -- I believe you mentioned before the Tapentadol hydrochloride was one of those compounds, right?

A. Yes, this is correct.

Q. What was shown with regard to Tapentadol hydrochloride, was that necessary data?

A. Based on all the different evaluation manuals with different scoring and weighting of such values in all exercises being 200 was selected was ranking in Number 1.

Q. Now, could we see PTX 597, maybe 597_T.

MR. BEST: And for the record this is trial exhibit PTX 597_T beginning at GRTNUC 150195_T.

Q. Are you familiar with this document?

A. Yes.

Q. When is it dated?

A. This is dated on the 29th August in 1997.

Q. If we could look at the page marked 150198, the paragraphs under the heading Human Pharmacology and

Pharmacokinetics.

Could you explain for the Court what is discussed here?

A. Here the pharmacokinetic profile of the compound is investigated including clinical data. What we have seen before in animal models, there was analgesic activity tested giving the dose in an oral way and of course also I.V.

However, in the different animal species we have used at this time there was, let me say, a much lower ratio in terms of orally, of oral activity in comparison to the I.V. activity.

And here for the first time it is shown that the animal data in mice, rats and dogs used at this time were not correlating to the clinical situation. Because here it is shown that in humans bioavailability of 32 percent is achievable giving the range between 42. The clinical is quite an amazing ratio that pharma companies would never decide to go for a compound that's a ratio between PO and IV activity is having I like to say two digit of differences which was in fact the case for Tapentadol.

And the 32 percent given here is indicating that 32 percent of the total amount of the compound given to a human being is available in the system. And this means this 32 percent is unable to treat pain symptoms. And this was one of the most amazing situations that there was a non correlation between animal data and human data in this case favorable that the species human being was much better having a much higher

bioavailability than the used animal tested so far.

Q. What if any impact on Grunenthal's plans for Tapentadol did this 32 percent oral bioavailability have?

A. This was an indication that the further clinical development was possible because it was demonstrated that sufficient oral availability in humans is possible.

Q. Now, going into these clinical studies, were you still synthesizing all the Tapentadol that Grunenthal was using?

A. Of course not because the synthesis of samples better used for clinical trials have to be synthesized and manufactured according to the international guidelines on the G.N.P. conditions which is not possible in a normal lab.

Q. Where at Grunenthal or in what part of Grunenthal were the syntheses of these amounts made?

A. This was done in two departments, one, the process development department which were looking for scaling up and the pilot plan that means in the German nomenclature it was culled chemische and entwicklung and which means chemical development that goes from smaller amounts to bigger and bigger amounts to be synthesized.

And using also bigger reactors not only at two different flasks but also then 50 or a hundred liter reactors. It means the engineering in upscaling was done there.

Q. There's another term for that process, "process chemistry"?

A. Yes process development, process chemistry, upscaling, pilot plant scale. A lot of different terms are existing.

Q. The process chemistry or process development department continued to use the method of making Tapentadol that you developed in your lab?

A. Normally if you go for upscaling the original root used in the medicine or chemistry department is changed in terms of increasing the chemical yields using for environmentally safe solvents and so on. So. It's really then a reprocessing of the chemical synthesis to maximize the yields and to minimize the cost investment for the different reagents.

Q. I think you said --

A. And of course to achieve the right quantity.

Q. And I think you said that's typical. Was that also performed for Tapentadol?

A. Exactly.

Q. Now, in addition to, or once you had started Tapentadol into this clinical development, did you further characterize the physical, any physical characteristics of the compound?

A. Yes. And this time it was considered important also to take consideration of the so called solid phases of the compound intended for oral use.

Q. When you say the 'solid phases of the compound', are you referring to it's crystalline character?

A. Solid phase means crystalline or amorphous character as

well as different salt forms that means any possibility to bring the Tapentadol base to a solid, to a solid was investigated. And the scientist also investigates the hydrochloride salt if different polymorphs may exist.

Q. And did you have a role in helping to examine that question whether different polymorphs existed of Tapentadol?

A. So at this time I was appointed to head of chemical research. And at that time I started the discussion at Grunenthal that this kind of solid phase investigation is important for any further development. And as a consequence also then we started with a lot of discussion with management the investigation of the solid phases in terms of polymorphic investigation and screening.

Q. Do you know Michael Gruss?

A. Yes, I do know Michael Gruss.

Q. Who is he?

A. He was, he is a chemist which was hired at Grunenthal. In fact, he was hired by me to support the chemical department.

Q. And was he or did he have a role in this examination of the polymorphic character of Tapentadol hydrochloride?

A. Based on his university background as an inorganic chemist, first he was the inorganic chemist employed at Grunenthal and with his previous experience at university was Telegraphy (sic). He was the right person to start these activities.

Q. Did you have to do any convincing to get Grunenthal to hire him?

A. There were several discussions necessary to convince management that an inorganic chemist may make sense to be employed at Grunenthal at this time.

Q. Why was that?

A. Because at this time only organic chemists which have education to synthesize organic compounds were considered as the relevant ones looking for new compounds with new activities.

Q. I think you testified earlier that you left Grunenthal in 2002. Is that correct?

A. This is correct.

Q. Before you left Grunenthal, did Tapentadol go into clinical trials?

A. This is correct.

Q. And did those trials conclude before you left the company?

A. These were trials which were ongoing.

Q. Did those trials ultimately end up supporting approval of Tapentadol as a marketed product?

A. At the end these trials were supporting the approval. This was the reason why it was approved using this clinical data.

Q. When did you first learn that Tapentadol hydrochloride

would be sold as a new analgesic?

A. Looking to the press releases and the information at Grunenthal.

Q. How did that make you feel?

A. I was quite proud because a part of my early research was further developed and then it was possible to see a compound with some properties which may be used to treat pain. And to see such a compound in a pharmacy, of course, makes you quite proud because this happens not too often in the life of a chemist.

Q. We have PTX 534_T.

Do you recall we looked at this document earlier? It's marked GRTNUC 66491 and the statement of Professor Strassburger. And I think you testified that he was doubting at the time that there were, that there would be success in meeting these four goals.

Do you recall that?

A. Yes, I recall it.

Q. Was he correct in his assessment?

A. At this time based on the data available he was correct. But then it was demonstrated that a solution was possible some weeks later or a short time period later the synthesis of Tapentadol had taken place and then investigations were taken place.

And at the end it was demonstrated that these items,

this one molecule oral availability one enantiomer no active metabolites and most important one to have post mechanism of one molecule unified was possible.

Q. Does Tapentadol hydrochloride possess all of those characteristics?

A. I would consider definitely yes.

Q. Could we see PTX 630? Do you recognize this document?

A. Yes, I do.

Q. What is it?

A. It's the revenue article to retrospective view on the differentiation of Tramadol and Tapentadol covering different activities from structure comparison to pharmacological comparison.

Q. And when you say a retrospective article, what do you mean by that?

A. Taking all information available at this time, that means 2012, into consideration and to try to tell and to summarize, based on all available effects during all the long time of development together to make a story out of it and to give some explanations to other experts in this field.

Q. And are you an author of this article?

A. I was a co-author of this article.

Q. Could we have the split screen of what was internally marked originally in the document as Page 1440 and 1447? These for the record are GRTNUC 183851.

THE COURT: What does that translate into in my book, defendant --

MR. BEST: This is PTX 630 and it's.

THE COURT: I have 630. Was there another one as well?

MR. BEST: Just two pages of the same document. Just a moment.

THE COURT: Okay. Is it 61 and 63?

MR. BEST: It should be, yes, it's 61 on the left and on the right hand.

THE COURT: Is that 63 on the right?

MR. BEST: It is but it should be 68.

THE COURT: 68. All right.

Q. Could you highlight please the heading, just the heading? And then on the right-hand side.

Now, you have this section entitled, Tapentadol as a rationally designed poly pharmacological ligand.

Do you see that?

A. I see that.

Q. Can you explain what you meant by rationally designed in this context?

A. So, at the time we tried to explain that we were considering a step-by-step investigation of structural variation. And to investigate the pharmacological inference of this structural investigation through the rationale design was

taken, was meant in a way to take incoming information and to understand incoming information in terms of pharmacological activity to design as the next variation based on this rationale which you have learned from the previous experiment.

Q. And in this final summary paragraph of the document there's this notion of an iterative process?

A. Exactly.

Q. Does that relate to what you were discussing?

A. Yes because of one structural area experiment to learn what is inference and outcome of this experiment. And to take these results into consideration for designing and to making the next step, step by step in iterative way.

Q. Now, may I direct your attention to Figure 1 of the document which is on 183861 which I think you already have up on the left?

Now could I ask you to discuss what is shown in this figure?

A. So, this is trying to summarize all the different points where you can make variations of the starting concept Tramadol to make variations. So, it is the characteristic summary of structural variances done in this Tramadol successor project.

Q. When you say the variations done in the Tramadol successor project, does that refer to the several hundred compounds you were discussing earlier?

A. Exactly.

Q. Now, could I ask us to look at Page 66. I believe it is, I'm sorry, 67 and the discovery of Tapentadol.

Do you see the first sentence of this paragraph? Could you read that for the record?

A. Yes.

Q. Could you read it into the record please?

A. The discovery Tapentadol involved multiple steps of chemical innovations to become a unique drug.

Q. And what did you mean by that?

A. So that the starting point Tramadol was considered as the basis. And then that it was possible at the end to have the iterative process to going from molecule to molecule and investigating the pharmacological properties to end up with a molecule which was fulfilling most of the items which were known as the desired items of the successor Tramadol project.

So, it was still unique and still fascinating for me today that it was possible that means going from a more complex structure with a quite complex profile of pharmacological activity, enantiomers and contributing of enantiomeric metabolites to end up with a smaller molecule having all these activities desired in the ratio without being a resume, without being a protract. It's still a fascinating thing to do even sitting here.

Q. Have you been recognized by others in the industry for

those chemical innovations?

A. After Tapentadol was on the market, I was awarded with IUPAC prize for the discovery of Tapentadol in 2014.

Q. I'm sorry, in?

A. In 2014.

Q. Could we see PTX 647? Do you recognize this?

A. Yes.

Q. Particularly the handsome fellow in the picture?

A. Yeah. It was a different time.

Q. What is this document?

A. This is a press release of the awarding procedure.

Q. And if you could blow that up please, Rob.

So, this award was given for the invention of Tapentadol. Is that right?

A. This is correct.

Q. And what is IUPAC?

A. IUPAC is the International Union of Pure and Applied Chemistry which is a worldwide organization covering Asia, America, Europe to bring all chemical activities under one roof.

MR. BEST: I have no more questions at this time. I would just like to thank you for your time.

THE COURT: Thank you very much. Much appreciated. Thank you.

Shall we begin directly with the cross or do you

want to take our lunch break? I can do either way. However you would like to handle it. I'm not sure whether I think it might actually be here. But if you want to start, that's fine. However you would like to do it.

MR. CAPUANO: I think we would rather have a lunch break first, your Honor.

THE COURT: Sounds good. You may step down. Thank you, sir. We are going to see you again today.

We are going to have a lunch break about 45 minutes. We can see. You should go back to the same rooms you had yesterday. I think it's fine as well.

(Lunch recess)

THE COURT: Any issues or should we go directly into cross? Anything? No. Let's begin. We can have our witness come back to the stand. I'll just remind you that you remain under oath. Thank you.

CROSS EXAMINATION BY MR. CAPUANO:

Q. Good afternoon, doctor.

A. Good afternoon.

Q. My name is Vince Capuano and I represent one of the defendants Actavis in the case. We thank you also for taking the time to come be with us for trial.

I want to go back to the Tramadol successor project and Grunenthal's beginning of that project. It's true, isn't it, that Tramadol was the starting point for that project?

A. The pharmacological activity of Tramadol was considered as a starting point, not the structured features. This is quite a big difference.

Q. And Grunenthal considered Tramadol the starting point even though it was a mixture of two isomers, correct?

A. The pharmacological activity was a complexity of the molecules of Tramadol of enantiomers. And metabolic enantiomers was considered as a starting point.

Q. And you'd agree, wouldn't you, that Tapentadol was the product of the rational design based on Tramadol. Isn't that right?

A. This is completely not correct.

Q. Okay. Let's look at plaintiff's Exhibit 1051. You know what, I need to pass out some books.

THE COURT: Any issue with the exhibits?

MR. BEST: No problems here.

THE COURT: Just let me know at any point if you need to you stop for sealing purposes. Is there anything that you anticipate?

MR. CAPUANO: I do not, your Honor.

THE COURT: All right.

Q. Dr. Buschmann, do you recognize this book entitled Analog Based Drug Discovery III?

A. Yes, I do.

Q. And in fact you wrote a chapter in this book. Isn't

that right?

A. This is correct.

Q. And that chapter is shown here and it's included in your book as exhibit, plaintiff's Exhibit 1051. This book was published in 2013.

Isn't that right?

A. This is right.

Q. Now, if you turn to Page 302 of the chapter you see a heading there 12.2 The Discovery of Tapentadol?

Do you see that?

A. Yes.

Q. And at the beginning of that section starting with Based on, do you see where you write "Based on elucidation of the favorable aspects of the multimodal analgesic mechanism of action of Tramadol, a research program was initiated in the late 1980s at Grunenthal".

Do you see that?

A. I see that.

Q. That's the Tramadol successor project at Grunenthal, correct?

A. This is correct.

Q. And at the bottom of that same section you see there "Tapentadol is an example of a rationally designed multiple ligand starting from the Tramadol structure", right?

A. This is right.

Q. So, is it still your testimony that Tapentadol was not rationally designed starting from the Tramadol structure?

A. You have to understand what is the meaning of the rational design in this context. In Russia the meaning is the you have a rational with the structure variation coming to a conclusion not to have any prediction, this means step by step, to use experimental data for the following process.

Q. But, it was based on the Tramadol structure according to your writing, right?

A. This is a retrospective summary. It was not based on the Tramadol structure but on complex molecular activity consisting of enantiomers and metabolic enantiomeric contributions.

Q. Now, at the time you started working on the Tramadol success project at Grunenthal, Tramadol was the only analgesic that was known to work through a combination of opioid and non opioid mechanisms. Isn't that right?

A. As far as I could recall that may be right.

Q. In fact, among the many analgesics known at the time and developed throughout the history of the treatment of pain, only Tramadol was known to have this unique combination of opioid and non opioid mechanisms of action. Isn't that right?

A. I wouldn't say this can be stated as a general statement. You have to look to the full file of all known energy compounds known at this time.

Q. But, you're not aware of any others, other than Tramadol, are you?

A. At this project I was aware about Tramadol.

Q. Right. You're familiar with Dr. Friderichs as well? He is one of the co-inventors on your patent. Isn't that right?

A. This is right.

Q. And did you read the transcript of Dr. Friderichs' deposition?

A. I haven't read the transcript of the Dr. Friderichs' deposition.

Q. Fair enough. Now, in terms of the structure of the new compounds that Grunenthal was making in the Tramadol successor project, the focus was to start with Tramadol and systematically vary the structure of Tramadol.

Isn't that right?

A. That was not right. This I was trying to use the pharmacological activity and in the mechanism action of Tramadol as the starting point.

Q. Let's have the Tramadol successor brochure DTX 1027 and let's look at Page 11. Let me just blow up that structure.

You looked at this on your direct examination by Mr. Best. Do you remember that?

A. This is correct.

Q. This states Tramadol is characterized by three

structural elements, A, B and C. Do you see that?

A. This is correct.

Q. Okay. And those elements, and you talked about this a little bit, A is circled here. It's the aromatic ring, correct?

A. This is correct.

Q. And just very basically this is aromatic, why would you call this an aromatic ring? Just for the Court.

A. Because of the electronic distribution of the electrons within the set molecule having been available and having structure and according to the aromatic rule was set to 2N plus two rule.

Q. And another one of the structural elements of Tramadol is structure B which is referred to as tertiary nitrogen atom, correct?

A. This is correct.

Q. And the reason it's called -- let's start there. The reason it's called tertiary nitrogen atom is because it has three substituents attached to it, correct?

A. This is correct.

Q. And if one of those substituents was taken off and replaced with hydrogen, we would call it a secondary nitrogen atom?

A. This is correct.

Q. And if we took off two of them and replaced two of them

with hydrogen, we call it primary nitrogen atom or primary amine, correct?

A. This is correct.

Q. And you agree that for Tramadol -- well, let me go back one step.

The two substituents that are on this nitrogen are what we call methyl groups, correct?

A. The dotted lines could mean anything. It's just indicating it's a tertiary amine. It's not written as methyl groups.

Q. This is Tramadol, right?

A. This is considered as a basic concept of Tramadol. This is the reason why dotted lines are included.

Q. This says, as shown in Figure 3 using the example of the Tramadol molecule, this is what this is, the Tramadol molecule, isn't it?

A. This is the Tramadol molecule.

Q. This is the Tramadol molecule. This is the methyl group, right?

Q. A methyl group is a single carbon atom with three hydrogens on them, correct?

A. This is correct.

Q. And you agree that for Tramadol this dimethylamino group was essential for its activity at the opioid receptor, correct?

A. This is not correct.

Q. Okay. Let's look at -- do you remember answering that question at your deposition and you said that the tertiary amine was responsible and essential for the Tramadol molecule?

A. This is correct but this is not a contradiction because also other substituents may be responsible, contribute to the opioid receptor because the metabolites identified in the Tramadol case is contributing to the metabolic activity. It's considered tertiary. The methyl group was considered as a good group.

Q. Just as a good group?

A. Yes.

Q. You think you could have taken off one of the methyls and it still would have had activity?

A. This has to be tested.

Q. I agree. Let's look at the 1978 Flick paper. It's DTX 834.

MR. CAPUANO: And I'll just note for the record that DTX 834 is a poor photocopy of this English translation of this paper. And so what we've used as a better copy is what we used at the deposition of one of the experts, Dr. Roush. This is Dr. Roush Exhibit 108 from his deposition. It's the same as DTX 834.

I communicated to plaintiffs that we were using the Roush exhibit rather than the particular DTX 834.

Q. You're familiar with Dr. Flick, correct?
A. No, I have never met him.
Q. But you know who he is, don't you?
A. I was informed who he was.
Q. And he is the inventor of, one of the inventors of Tramadol, isn't he?
A. He was one of the first connected who was first synthesizing Tramadol as the complex mixture of diastereomers.
Q. You've seen this paper before from 1978, haven't you?
A. I have seen this paper.
Q. It's one of the papers that you were studying as part of the Tramadol successor project, wasn't it?
A. This was available but I have not studied it.
Q. You didn't look at it when you were working on the Tramadol successor project?
A. Yes, I looked at it.
Q. This paper reports on the structure activity relationships for Tramadol and molecules related to Tramadol, doesn't it?
A. Yes.
Q. Okay. Let's turn to table three in this paper and I really just need the top. Well, that's good. That's fine.
Can you see table three?
A. Yes.
Q. You see Table 3 has a structure at the top, a generic

structure at the top. Let's just go back to the table.

You see for the compounds that were presented in Table 3 there's a group R1. Do you see that?

A. Yes.

Q. R 1 is the group on the aromatic ring, correct?

A. This is correct.

Q. And for all of the compounds in Table 3, R1 is the same group it's what's denoted as m-OCH3, correct?

A. This is correct.

Q. Okay. And the OCH3 is oxygen and a methyl group, correct?

A. Right.

Q. And the M is a designation of what we call meta, right, m-e-t-a, correct?

A. This is correct.

Q. And that means, it's on the third M just means that it's on the third position on this ring, correct, starting from where it's attached 1, 2, 3, it's on the third position, correct?

A. This is correct.

Q. Every single one of the molecules studied in this table have that same substituent at the aromatic ring, correct?

A. This is correct.

Q. Now, R4, I'm sorry, this is R2, is this position?

A. Yes.

Q. Right there, correct?
A. Correct.
Q. That's what we sometimes call the aliphatic carbon position on Tramadol. Is that right?
A. The aliphatic carbon position?
Q. Strike that. It doesn't matter.
For the compounds presented in Table 3 for R2, every single one of those is a hydroxyl group OH, right?
A. This is correct.
Q. Okay. And so what's being varied here in this comparison are the groups on the nitrogen, right, R3 and R4?
A. This is right.
Q. Do you agree with that?
A. Yes.
Q. And in particular what's in the table as L201, this is Tramadol, isn't it?
A. No, this is not correct.
Q. This is not Tramadol?
A. Because the L code was referring to a diastereomeric mixture but the L code was indicating, for example, it was coming from the labs of Dr. Frick and it was later reviewed. It was quite a complex mixture of all four stereoisomers of Tramadol.
So what is sitting here is a result of a grignard (sic) and not the Tramadol because the other diastereomeric

enantiomers were included and measured which were not known at this time.

Q. You agree that L201 includes Tramadol?

A. This I could say, yes.

Q. Okay. And what Dr. Flick did in this paper is he looked at what happens when you change the groups on the nitrogen, right? That's what's being studied in Table 3, isn't that?

A. Yes and some variations which are reported in this table.

Q. In particular just above the 201 is B419 where he took off one of the methyl groups and replaced it with hydrogen, correct?

A. This is correct.

Q. Okay. And above that is B450 where he took off both methyl groups and replaced them both with hydrogen, correct?

A. This is correct.

Q. Okay. Now, what he did -- and then he did some other things to vary it in other ways below that. And for each of the compounds presented in Table 3, he looked at the analgesic activity in a particular mouse study and that's presented in the column called analgesic activity.

Do you agree with that?

A. No, I don't agree with that because the only thing you saying is this other methyl pharmacological data offset any

minimum which was used under these conditions.

Q. You agree that he studied these compounds in an animal model, correct?

A. Which is indicated with the ED50.

Q. That is an animal model for analgesic activity, correct?

A. I can't recall what the offset animal model was used in this paper.

Q. Well, let's look at that. On the previous page there's a Section 3.1.1. Do you see that?

A. Yes.

Q. This is the testing that was done is testing for analgesia according to some method of what's indicated here as Kraushaar.

Do you see that?

A. Yes.

Q. We can read this together or you can read it yourself. But, what it indicates is that analgesia testing was performed on a group of mice.

Do you see that? And it says per dose at 30 and 60 minutes after oral administration of the substance, that would be, the substance would be the different compounds that are being tested, correct?

A. Yes.

Q. And then it says pain stimuli applied were direct

current pulses of a certain intensity and duration repeated at every second at 1 second intervals.

Do you see that?

A. Yes, it see this.

Q. And it says the stimulating electrode used was the tail clamp and the counter electrode was the metal sleeve used for positioning the animals.

Do you see all of that? Do you understand --

A. I see.

Q. -- how that test was being done by that description?

A. This is a description of a test model. And this is a test model which was used at this time but later was considered giving electro stimulus to an animal is not really a pain model.

So what we will only seeing is using this test model giving electric stimuli to the animal we are resulting in this data. But, this for an expert now in this mode starting some years later never would have done such a pain model.

Q. But, the authors of this paper believed that it was one way to test for analgesic effectiveness, correct?

A. At this time it was considered, yes.

Q. Okay. And what they determined from this test is what they call an ED50 value for each compound. You see that?

A. I see this.

Q. And you have an understanding what ED50 is? You talked

about it this morning, right?

A. Right.

Q. What is your understanding of what ED50 means?

A. An ED50 is the dose dependent dose, the point, a state of mind as the amount of compound per 50 percent of energy effect foreseeable.

Q. Just in general terms for ED50, the lower you make the ED50 value, the more effective the compound is an analgesic, correct?

A. This is correct.

Q. So, let's turn back to Table 3. And you can see for L201 where there is two methyl groups on the nitrogen, the ED50 is reported at 16.1.

Do you see that?

A. I see that.

Q. And no matter what else was done in this series of compounds to the nitrogen group, the effectiveness for analgesic activity went down for every compound, isn't that right?

A. Under the tested conditions using this test model given oral application, you have to consider if you would like to learn something out of this data.

Q. You agree that the effectiveness for analgesic activity was the test that was applied here went down for every compound that wasn't a dimethylamino group, right?

A. This is right.

Q. And so let's look at the conclusions that were drawn by the Tramadol inventors based on this comparison. Let's look at section 3.2.1 of this paper.

Here in this section the authors are discussing what happens when you vary the substitution on the amine nitrogen and they refer to Table 3, correct?

A. This is correct.

Q. Okay. And they say in group one those are the compounds studied and presented in Table 3. Only the dimethylamine derivative L201 has strong analgesic activity. This is already lost entirely when only one methyl group is replaced by a hydrogen atom. And refer to compound E419.

The bis-desmethyl derivative E450, that's one without any -- with both hydrogens replacing the methyl, correct?

A. Correct.

Q. Is also inactive as an analgesic. Do you see that?

A. Under these test models used.

Q. They also talk about other replacements for the dimethylamino group. These are the other things that are presented in Table 3. And they say that they are all inactive analgesics with this test, correct?

A. Under these test conditions, yes.

Q. Can we put up, I want to look at Mr. Fitzpatrick's opening slide Number 36 from yesterday.

You recognize the top two structures here to be the mixture of RR and SS Tramadol enantiomers that was presented in Tramadol, correct?

A. Correct.

Q. Okay. Now, one of the differences between Tramadol and Tapentadol is that this hydroxy group, this OH group is not present in Tapentadol, correct?

A. This is one of the differences.

Q. All right. And in your view nobody would have been able to predict that you could make this substitution and still maintain analgesic activity, right?

A. Yes.

Q. You testified that way in your deposition, correct?

A. Yes. And I would even repeat it today.

Q. Very good. This substitution was one of the substitutions that Dr. Flick studied in 1978. Do you recall that?

A. If he used any metadata he has presented.

Q. And you know that when this substitution hydroxyl on this position was replaced with hydrogen in the 1978 paper, it showed that there was still strong analgesic activity for the hydrogen replacement compound?

A. This was a substitute of compound investigated. It was not clear what really compounds were measured at this time. So, a lot of time went through after starting in '92 the

process and a lot of additional information were discovered at Grunenthal.

And even this paper was not considered as a starting point because it was misleading with all data coming in, but, was preparatory knowledge of Grunenthal.

Q. You don't disagree about the data that's presented in the 1978 paper, do you?

A. So, it was not considered as a valid starting point because experimental conditions and the ways the compounds were tested and synthesized, you are not considered as appropriate with forthcoming methods used at this time an indicated with the old codes. And with L and E codes you get complex mixtures of compounds.

Q. Do you agree that the compound tested by Flick were hydroxy, when replaced with hydrogen, showed strong analgesic activity?

A. This is correct.

Q. Let's take a look at Flick again.

THE COURT: Can we just get an actual date for this Flick argument, I mean this paper, rather.

MR. CAPUANO: 1978, your Honor.

THE COURT: Does it have a date on the document?

MR. CAPUANO: I think on the original German document. This is a translation.

THE COURT: So sometime in 1978.

MR. CAPUANO: It was in 1978. The original German is more specific.

THE COURT: What is the other exhibit. This is the same exhibit, not the Roush 108. Do you know what it is?

MR. CAPUANO: It's defendant's Exhibit 834. That exhibit has the English and the German together. The English photocopy is not good.

THE COURT: Is the date on that document, do you think?

MR. CAPUANO: It's on the German.

THE COURT: It is. All right.

Q. I just want to round out this point. I want to compare L201 in Table 3 with E609 in Table 4.

In any case, you see the change here? L201 has the hydroxy as that carbon and E609 has the hydrogen, correct?

A. Correct.

Q. Otherwise they are identical, L201 and E609, correct?

A. Correct.

Q. Okay. And the ED 50 3609 is 23.6 milligrams, correct?

A. Under these test conditions it's a mixture of compounds which were tested. And in this case E609, which was a year later, was not only the nitrogen compound, it was used from the aliphatic compound which is hydrogenated. It was also double bound compounds included.

So, this is a mixture of experimental procedures which you can't reveal that hydrogen substitution is giving this value. And this was not taken into consideration. This was knowledge which was coming after the paper in '87.

Q. There is nothing in this paper that indicates that E609 is anything other than what's listed in this table?

A. This is right. But, with the follow up information after 4, 5 years more research, this was revealed and that was the basis we took in consideration as a starting point. And even be considered after this 550, different compounds which were already synthesized before I joined Grunenthal.

And this information was quite different which was summarized here which was thus compiling subsets of all compounds 25 and 27. And we haven't used it because knowing now how well is this data are not of any relevance.

Q. But, the information you know about E609 and L201 is not information that's available to the public, is it?

A. I don't know. I don't think so.

Q. On the second to last page of the English Flick there's a paragraph that starts In contrast to. There you go.

Now, the conclusion these authors make from replacing that hydroxyl group with hydrogen is that in the case of the cyclohexanes, the bridge carbon may also be substituted with a hydrogen atom without this being associated with a substantial loss of activity.

Do you see that?

A. Yes.

Q. And that is not the same as your opinion that if you had made this change you could never have expected there to have been analgesic activity, right?

A. Based on the compounds afterwards, this was not expected.

Q. But, based just on this paper, this public paper in 1978, you would have thought that replacing the hydroxy with the hydrogen would have still maintained strong analgesic activity, right?

A. If all other features which are possible to change maintains the same, this could be concluded how it is written there.

Q. Now, one of the other things you testified about at your deposition, you testified that the most surprising thing was that in terms of stereochemistry, you achieved opioid activity of Tapentadol having what you call the wrong stereochemistry.

Do you remember that?

A. The wrong stereochemistry in terms of systemic chemistry according to the enantiomers. So what we are talking about is still a complex mixture. We are thus talking about one substitution without taking into account all other relevant aspects which are known today.

So that means whatever conclusion you are taking out of this single exchange, doesn't mean that it's reality because all other information you have to consider.

Q. Okay. And we're going to consider that other information now. Let's turn to Mr. Fitzpatrick's 36 again.

Here are the two enantiomers of Tramadol, correct?

A. Correct.

Q. And the one on the right is what we've labeled SS Tramadol. Do you agree with that?

A. Yes.

Q. Okay. And so what you're saying is that well, you agree that SS Tramadol has the same absolute stereochemistry as Tapentadol, right?

A. If you refer to the absolute sense of stereochemistry, yes, independent of the descriptors.

Q. Okay. And your point at your deposition was SS Tramadol has almost no opioid activity. Isn't that right?

A. This is right.

Q. And you were very surprised and thought it was the most surprising thing that Tapentadol, having the same absolute stereochemistry, has good opioid activity, right?

A. This is correct.

Q. That's the point you were trying to make at your deposition, isn't it?

A. Yes.

Q. Okay. Well, let's look at the metabolites. The SS O desmethyl Tramadol shown here on the bottom right also has the same absolute stereochemistry as Tapentadol, right?

A. Right.

Q. And this compound does have good opioid activity, doesn't it?

A. No.

Q. Okay. Let's look at --

A. In comparison to the other enantiomers if you compare activity, you have to also read what is the main contribution of the enantiomers. And so the opioid affinity is in the plus enantiomers of Tramadol.

Q. Are you saying that the SS O desmethyl Tramadol doesn't have any opioid activity?

A. No. I'm saying the opioid activity of the plus enantiomer of the plus metabolite is making orders of higher than minus one. This is what I'm saying.

Q. For Tramadol?

A. No, to the Tramadol metabolites you are referring to. We are talking about the SS and RR O desmethyltramadol. This is correct?

Q. Yes, that's right. We're talking about SS O desmethyl has opioid activity, right?

A. I can't claim the number what is the opioid affinity. I am only telling you the relationship of or ratio between the

plus Tramadol RR Tramadol is a much more stronger opioid than the minus one. The opioid affinity a minus metabolite was never detectable in vivo.

Q. These two compounds, the SS metabolite and the RR parent compound of Tramadol, these two compounds were described by 1993, a year before you filed your patent application, these compounds were described as having both opioid and non opioid analgesic activity. Isn't that right?

A. I don't know where it was described. It was revealing that Tramadol is the product and that the metabolites are contributing to the activity. And if you describe the metabolite activity in Tramadol, you have to consider first the known enantiomers of the parent drug and the enantiomeric metabolites.

Q. Let me have defendant's Exhibit 736, first page.

Dr. Buschmann, are you familiar with this paper?

A. I can't recall it but I can now read it.

Q. Well, I'm not going to ask you to read the whole thing. I'm just going to point out to you that this is a paper that was published in 1993. That was before you filed your patent application in 1994, correct?

A. Correct.

Q. Okay. And if you look at the title to start there, this is talking about effects of the central analgesic Tramadol and its main metabolite, O desmethyltramadol in a certain

assay, correct?

A. Correct.

Q. Okay. And one of the conclusions, and we can just take that conclusion from the abstract Number 8, says here the last sentence there, The effects of plus Tramadol and minus O desmethyltramadol consist of combined MU opioid and alpha 2 adrenergic components.

A. I see that.

Q. These two compounds were described in 1993 as having a combination of both opioid and non opioid activity in that assay that was used, correct?

A. I assume, yes.

Q. And --

A. However, I have to mention, first of all, it's not the Grunenthal paper. And secondly, based on the in vitro measurement of opioid affinity with the data if Grunenthal used there is no relevant opioid affinity of minus metabolite of Tramadol.

Q. Lets's take those two, one at a time. You discount the paper because it's not a Grunenthal paper?

A. No, I haven't said. I'm only mentioning please remember this is not a Grunenthal paper and I don't know for what source this data are coming. And based on the internet information we have the Grunenthal, and this is also packaged in many other papers.

There were opioid affinities measured for the different enantiomers and the enantiomeric metabolite not only just for the O desmethyl metabolite. And here the main activity is a plus Tramadol metabolite and in minus metabolite it is effective of some hundreds higher affinity in you minus. And the smaller affinity doesn't mean it's of relevance whatever the authors are concluding.

Q. The papers that you are talking about did not appear prior to 1994, did they?

A. I can't tell you. So there are several papers around about Tramadol, of course.

Q. And the information you're talking about internally at Grunenthal is not something that would be available to the public, correct?

A. This I can't tell you because I was not aware it was published before '94 of this research project. But, as a research group, it was clear what was the data. And we are using this data which are relevant. It would be generated in our labs and discriminating the enantiomers in terms of opioid effect and non opioid effect, this was a major research activity at this time.

Q. You will agree that in 1993 published literature, the literature available to the public described that these two compounds individually, not as a mixture, but individually possessed both opioid and non opioid activity. Isn't that

right?

A. This I haven't understood this a sentence you have highlighted.

Q. You don't understand the sentence I highlighted?

A. I haven't understood this conclusion you have taken from the highlighted sentence. This is different.

Q. The sentence is a conclusion in the abstract is the effects of plus Tramadol and minus O desmethyltramadol consist of combined MU opioid receptors and alpha two adrenergic components. Do you see that?

A. Yes.

Q. What does this mean, MU opioid components?

A. This is opioid components for whatever molecule. I can't say this. And I can't reveal it just because it's highlighted sentences. And the other effect is alpha two adrenergic components is quite different effect which was also measured for several other molecules. And it is something which is related to a specific structure. But, it doesn't mean it has a contribution to what I read here plus Tramadol and minus O desmethyltramadol, it's opioid and alpha 2 adrenergic components.

And if you consider tramadol and tramadol metabolites, it is never considered an alpha 2 adrenergic component based on the relevance.

So, this author may have used the effect to make a

story out of it, but, it was without any relevance. Because the metabolites in Tramadol are not the alpha two adrenergic compound.

Q. Wasn't known as of 1993? That's something you know based on your internal information from Grunenthal, right?

A. Even a scientist, if you read through how it was measured, I don't know, I am only a chemist. I am not a pharmacologist. I can only conclude what was the basis of our research projects and shed some light on the data which was generated in our labs.

And the alpha adrenergic effect also was considered as one option based on the clonidine activities as an analgesic principle. But, this Tramadol translatable alpha two adrenergic was never foreseeable in our hands.

Q. This conclusion begins, The results confirm that the analgesic action of Tramadol involves both opioid and non opioid components. Do you see that?

A. I do see that.

Q. You'd agree with that even today, wouldn't you?

A. Yes.

Q. It appears that minus Tramadol inhibits the uptake of noradrenaline and via a subsequent increase in the concentration of endogenous noradrenaline indirectly stimulates alpha 2 adrenoceptors.

Do you see that?

A. Yes, I see.

Q. They are talking about stimulation of alpha two adrenergic receptors and the consequence of inhibiting the uptake of noradrenaline, right?

A. This is the conclusion of this also.

Q. They are saying that the stimulation of alpha 2 adrenoceptors relates to the non opioid components of Tramadol. Isn't that right?

A. It is written as alpha 2 adrenoceptor activity is considered as non opioid activity.

Q. Right. And they are saying that the effects of the plus Tramadol and the minus O desmethyl consist of the combination of these three components, right?

A. You can interpret it in that sense, yes.

Q. Your view is that Tapentadol is the first compound to possess both opioid and non opioid analgesic effects in a single molecule.

Isn't that right?

A. No, this is not right. This is the first molecule having MU opioid affinity and no automatic uptake effect in one molecule. The uptake effect is the non opioid component. But, you have to be more precise.

So, I'm not saying having an opioid or non opioid compound. It's the first molecule in one enantiomer having opioid affinity and no adrenergic inhibition effect.

Q. And the paper we just looked at talked about the noradrenaline uptake inhibition of these two compounds, right, RR Tramadol and SS O desmethyltramadol, right? Correct?

A. If you interpret it in this sense, yes. But, if you can conclude it, it would be necessary to read the complete paper. And whatever is written there, you have also to justify any scientific paper may have a wrong conclusion.

Q. Understood. I'm just trying to explain what the paper -- I'm trying to show you the paper.

A. Yes.

Q. The paper says these two compounds have a combination, each of them individually, of opioid and non opioid components.

Wouldn't you agree that that's what the paper says?

A. I can't say. It's a summary of the abstract and this doesn't mean that where you can't conclude it is really the case. I can't judge it. I don't know it.

Q. You agree that the abstract says it, don't you?

A. I can only read the abstract.

Q. And based on the abstract it tells you that these two compounds individually have both opioid and non opioid components?

A. This is a summary of the paper where it is the overall conclusion. And you can only make a judgment after you have read the paper and analyzed the data presented in this paper. And then you can agree if the abstract is right or not.

The only thing I can see it's written there, that doesn't agree with the content. This is different.

Q. Based upon -- sorry.

A. This is different.

Q. Based on the conclusions in that paper, Tapentadol is not the first compound to have both opioid and non opioid components in a single molecule. Isn't that right?

A. Tapentadol is the first compound having opioid affinity and noradrenaline affinity in one molecule in a balanced ratio contributing to the analgesic effect. That means if you simply it, it's a compound having opioid and non opioid affinity.

Q. A balanced ratio is the way you put it, right?

A. In ratio relevant for the energies, analgesic activity.

Q. So, you are not saying Tapentadol is the first to have those two activities. You are saying it's the first to have those two activities in a balanced ratio. Is that fair?

A. Yes, this is fair.

Q. Okay.

MR. CAPUANO: No further questions.

THE COURT: Thank you very much.

MR. SCHULER: We are going to go around the horn.

THE COURT: All right.

MR. SCHULER: Your Honor, can I approach the witness and the bench?

THE COURT: Yes. And do we have different

binders?

MR. SCHULER: Yes.

THE COURT: Why don't you exchange them.

Q. Good afternoon, Dr. Buschmann.

A. Good afternoon.

THE COURT: Let's stop for one second. Any issue with respect these?

MR. BEST: If we could have just one more moment.

THE COURT: Yes. Go right ahead.

MR. BEST: As I understand it, your Honor, we have sort of competing translations of one of the documents. And one of the translations has been handed out. And we have the competing translation from plaintiff's Counsel. And we would like to distribute this one also. As I understand it from Mr. Schuler, he doesn't object to doing so.

THE COURT: All right. Is that it? You both want to submit your own translations? Is that it?

MR. SCHULER: I'm happy to. I'm going to mark this for identification. They didn't put it on their exhibit list so I have pre-marked it for identification as DTX 2002.

THE COURT: Your translation.

MR. SCHULER: Their translation.

THE COURT: All right. Their translation. What is the number, DTX?

MR. SCHULER: 2002. I will hand it up, if I can

approach.

THE COURT: Certainly. So, is there any issue then? We have both translations.

MR. SCHULER: I'm going to use theirs because I don't think there's a difference.

THE COURT: Any other issues with respect to these?

MR. BEST: We don't think so, your Honor.

THE COURT: No.

CROSS EXAMINATION BY MR. SCHULER:

Q. Good afternoon Dr. Buschmann.

A. Good afternoon.

Q. You have specialized expertise in something called specialized knowledge in the field of stereochemistry, correct?

A. I have knowledge in the field of stereochemistry.

Q. And stereochemistry refers to the spatial arrangement of the atoms, correct?

A. This is one aspect of the stereochemistry.

Q. And if a molecule has what you call two chiral centers or one chiral center, there could be multiple arrangements or at least two arrangements of those atoms in a three dimensional space, correct?

A. One chiral center is present normally you would have two enantiomer molecules with the opposite direction.

Q. In the body, I think you mentioned this on your direct

examination, in the body there are things called receptors?

A. Yes.

Q. And they have particular three dimensional configurations for accepting a protein or an enzyme, correct?

A. This is correct.

Q. And the three dimensional spatial arrangement of the atoms in a molecule could therefore influence how it reacts inside the body. Is that true?

A. This is oversimplification because on one hand your chiral center and chiral amino acids contributing to the protein which is called the receptor. And over this, you also have another type of chirality which is the super molecular chiral consisting of chiral molecules are arranged in the three dimensional space.

So there are multiple descriptors of chirality and not everything can be reduced to a chiral center of a given molecule.

Q. I'm not trying to reduce it. I'm simply saying one of the attributes of chemistry is that the spatial arrangement of the atoms may make a difference inside the body.

A. This is correct.

Q. Okay. And in the way that my right hand and my left hand, they are mirror images, correct?

A. This is correct.

Q. But we know that for instance my right hand is not

going to fit readily inside of a left handed glove, correct?

A. This is correct.

Q. Now, as a person with specialized knowledge in stereochemistry, it's your experience that it's not possible to predict the activity of structurally similar enantiomers. Is that true?

A. It depends on the information you have.

Q. Well, let's look at your deposition at Page 23. And if you could focus on my question starting at Line 17. And do you see that I asked you As a person with expertise in stereochemistry can you predict the activity of structurally similar enantiomers.

And I'm going to skip the objection. And then you said In my opinion it's not possible to have any type of prediction based on the three dimensional structure.

Did I read that question and answer correctly?

A. Yes, this is correct.

Q. Now, your view that a person cannot predict the activity of structurally similar enantiomers comes from your experience in chemistry, correct?

A. Yes.

Q. Now would you also agree with me, doctor, that chemical reactions themselves are unpredictable?

A. No. This is a sentence, what does it mean chemical reactions are not predictable,

Q. Well, you agree with that there are a number of factors that can cause the outcome of a reaction to be completely different from what was intended?

A. This happens in chemistry.

Q. Would you agree that a chemist cannot predict the end result of a reaction because there are just too many variables?

A. This is a statement I can't agree because it's always based on what information is available, what information of derivation you are doing and what is done before. So general hindsight in my opinion is not possible to give.

Q. If you could look at your deposition again, this time at Page 78. And if we could focus with the question starting on line 21 through Page 79, Line 2.

And do you see at Line 21 I asked you earlier I asked you whether you can predict and you interjected yes. And I continued, The end result of a reaction. And you said no, there's just too many variables.

Do you recall that?

A. Yes.

Q. Do you see your answer is Answer: This I recall, yes.

Did I read that question and answer correctly?

A. Yes.

Q. Now, one attribute of what we call the scientific method involves verification. Would you agree?

A. I agree.

Q. And there are a variety of techniques that people in your field of chemistry use in order to verify that they have synthesized a particular compound, correct?

A. This is correct.

Q. And I think you mentioned two of them on your direct examination, one you called hydrogen NMR, correct?

A. This is one spectroscopic method.

Q. Let's just spell it out for the Court. That's the nuclear magnetic resonance, correct?

A. Correct.

Q. And another one I think you mentioned carbon NMR. Do you recall that?

A. I recall that.

Q. And verification is needed because even if a scientist has a certain hope of what should be the outcome of a reaction, that outcome is, in itself, uncertain.

Can we agree on that?

A. Again depending on the information you have doing this reaction if you make a similar reaction you may know more than if you have no knowledge what you are doing. And even if nothing is reported in literature. So there are a lot of common known name reactions existing in chemistry where the outcome is clearly defined.

Q. I'm not talking about the grignard reaction. I'm talking about a novel compound. Is it your view --

A. Even if you apply a known reaction to make an unknown compound.

Q. But here even though it's not reported in the patent, you verified and the analytical department verified the structure of the compounds you synthesized, correct?

A. Correct.

Q. And the reason you did that is that despite your hope as to what you might synthesize, you need verification, correct?

A. This is correct.

Q. Right. Now, one attribute of an enantiomer we forgot to talk about is that they have certain physical properties, correct?

A. I wouldn't say this is correct because normally it's considered that enantiomers have the same physical chemical properties. But, you have to define what chemical properties you are referring to.

Q. Fair point. I'm sorry. One of the physical chemical properties that is common between enantiomers is they should have the same melting point, correct?

A. The melting point is one characteristic of a compound. But, it depends on so many factors. So normally to characterize a compound you will never take a melting point into consideration. It's one metal coming from all teams which is considered an important factor.

But, if you know how many melting points, if you go to the scientific chemical excerpt service just go to one any compound there you will find a long list of melting points contained in literature.

Q. I don't think that was my question. My question, sir, was would you agree that generally enantiomers, because they have -- let's speak clear. They have the same atoms, correct?

A. If they have the same other properties.

Q. I'm not asking about properties.

A. No, it really depends. Because if you talk about enantiomers, you have to characterize and to specify the properties of the enantiomers in terms of resident solvents. Other impurities may be contained in a very low percentage concentration. All those factors are contributing.

And even if you make a measurement, it's two different people, of the enantiomers, the outcome may be different.

Q. Sir, I am coming to that. I am going to see if we agree on something. But, enantiomers have the same number of atoms?

A. In theory they should have if they have exactly all other properties which are exactly the same which doesn't become necessary if you compare enantiomers.

Q. We will get to that.

Can we agree that enantiomers, this is known in the literature, do something to plain polarized light?

A. Yes.

Q. Okay. And specifically the two enantiomers of a compound should rotate the direction of a plain polarized light in equal but opposite directions, correct?

A. Correct.

Q. All right. And if I have a molecule with 12 atoms and it's enantiomeric, those two compounds shouldn't react to a melting point experiment in the same way? Can we agree?

A. Based on the comments I have done before.

Q. Let's look at the reissue patent. You talked about it earlier.

Can we put up DTX 1346. And if we could turn to column 19, and isolate lines 24 to 30.

Now, you didn't talk about this on direct but you understand there's a bracket on some of the nomenclature?

A. Yes.

Q. And you understand that's been changed?

A. Yes.

Q. Okay. And the change here, as you understand it, is to change the name of the configuration to 1R 2R, correct?

A. This is correct.

Q. And then there's a reference to MP that you understand to be melting point?

A. That is correct.

Q. And I think you mentioned this to the Court earlier

that this melting point is 168 to 170 degrees, correct?

A. This is correct as it is written here.

Q. Okay. And if we move to the bottom of the column 18, do you recall, Dr. Buschmann, that in your patent you also described an enantiomer of Tapentadol?

A. Yes.

Q. Okay. And here again you understand that the language has been changed so that this is now the 1S 2S enantiomer, correct?

A. This is correct.

Q. And the melting point data is in the patent for that enantiomer if we look at Line 10. And do you see that that is listed as the melting point of 194 to 196 degrees?

A. I see.

Q. And we can agree, and I can put them together, but you understand that those are about 25 degrees different?

A. Yes.

Q. Oka y. Now, Dr. Buschmann, do you recall that the melting points that's listed here of 168 to 170 degrees is about 30 degrees lower than the established melting points in the literature for Tapentadol hydrochloride?

A. This was not an established melting point in the literature.

Q. I'm sorry, I will rephrase that.

Do you understand that the melting point listed of 168

to 170 degrees is about 30 degrees lower than what you knew to be the established melting point of Tapentadol?

A. In comparison to the melting points given for the other enantiomer.

Q. Okay. But also in comparison to other data that Grunenthal obtained in the course of physically characterizing Tapentadol hydrochloride.

Do you recall that?

A. Yes.

Q. Let's look at that together. So this is DTX 1414. And doctor, do you see that this is listed as an IND amendment?

A. Yes, I see it.

Q. And do you see in the third line for Tapentadol hydrochloride?

A. Yes.

Q. And you understand what an IND is? It's an Investigational New Drug Application?

A. Yes.

Q. You understand that in the United States that's the first application to administer the compound to a human being?

A. I understand, yes.

Q. Okay. If we could turn to the Page 6 at the bottom just before selection of excipients. And, doctor, do you see that it reads -- well, let's ask you this, in your experience at Grunenthal was it fair to say that in this type of

regulatory submission, there was a goal of insuring that the data that was provided to the regulators was accurate?

A. I considered yes.

Q. And here it says Tapentadol hydrochloride exists as white to almost white crystals or crystalline powder. It has a melting point of 201 to 206 degrees celsius. Do you see that?

A. I see this.

Q. Now, it also says that it's white to almost white powder. Is that what you observed when you looked at they syntheses of Tapentadol hydrochloride?

A. You have here to refer to two different things. I would recall it was a white powder and the term white or almost white is coming from the regulatory guidelines how to describe the color of the compound.

Q. You never saw Tapentadol hydrochloride that was yellow, did you?

A. I can't remember that I have seen any yellow Tapentadol hydrochloride --

Q. Okay.

A. How much, it depends on what is --

Q. Just asking what you remember, sir.

MR. BEST: Your Honor, objection.

THE WITNESS: I can't remember yellow.

MR. BEST: He's standing on the answers.

THE COURT: I'm sure you're going to be able to

follow-up afterwards. So to the extent we have questions that are coming a little fast, you can certainly respond.

MR. BEST: Fair enough.

THE COURT: Before we go, did you want to finish your answer? Did you have anything further to say?

THE WITNESS: Because related to the color, it's quite difficult to make a universal statement if you are seeing it because if you have white, white is not only describing the color, it's also having a lot of more characteristics, how the light is getting to the powder. So the crystallization, the light which is coming through the window may have an effect on the color you see. It doesn't mean this color is really the color of the white powder you have.

Q. Now, would you agree this is not an spectrographic analysis?

A. Organoleptic related to the specifications needed for this document.

Q. Fair enough. So, now if we can turn back to your reissue patent which is defendant's trial Exhibit 1346, column 19 again. And if we could look at Line 30. There's a reference to an alpha symbol. Do you see that, doctor?

A. Yes.

Q. And is that a way that scientists in your field refer to the rotation of light?

A. This is optical rotation symbol.

Q. And the value reported here is 27.5 degrees in the negative direction?

A. This is the report.

Q. If we could look back, Mr. Haw, at Line 10.

Do you recall this is data for the other enantiomer?

A. This is correct.

Q. And then the alpha symbol here as a positive direction which is an L symbol which is the opposite direction from the minus, correct?

A. This is correct.

Q. And then here the degree of rotation is plus 24.5 degrees?

A. It's correct.

Q. Now, if we can turn to defendant's trial Exhibit 1350, this is what is called a declaration of power of attorney for a patent application.

Do you see that?

A. Yes, I see it.

Q. And if we go down a little further your name should appear?

A. This is correct.

Q. And you recognize this as the oath that you signed in connection with the U.S. patent application?

A. This is correct.

Q. Is it fair to say, doctor, that you would have reviewed

this application at around the time that it was submitted to the United States?

A. Yes.

Q. Now, if we can turn to the actual application which is defendant's trial Exhibit 950 -- I'm sorry if we can go back Mr. Haw, I forgot.

And if we could look at the oath itself and I'm just going to characterize. You can feel free to read it specifically.

But, do you recall generally what you said here was that you had reviewed the contents of the application before you signed the oath?

A. Yes.

Q. And it is accurate to say you did review the application?

A. That's the best knowledge at this time.

Q. Now, Mr. Haw, we can go to the actual application at Page 30. I'm sorry, we will look at the cover page just to make sure.

If we go to the next page, you do recognize this? And I'm happy, you can look at it in your binder. But, do you recognize this? Unfortunately the copy is not the best. But, do you see that it's the same application?

A. Yep, yep.

Q. We can look at Page 30 which should refresh your

recollection. Okay.

So, towards the bottom on line 28, do you see a corrected chemical name?

A. Yes. The first material commence descriptor was corrected.

Q. If we focus on what was printed before it was hand corrected, it was the 1S 2S designation, correct?

A. How it was written there, yes.

Q. And someone handwrote in 1S 2R. Do you see that?

A. I see this.

Q. And the purpose of naming the compound the 1S 2S name is to indicate the chemical structure, correct?

A. To indicate the chiral centers including in the chemical structure the chemical structure is named by the other name showing the constitution of the compounds. It means the order of atoms which are attached to each other.

Q. I think you just said this but hopefully we can agree, another purpose of giving it a name like 1S 2S is to give evidence of its stereochemistry, correct?

A. It depends what is the aim of the name. So, it is one measure. If you have nothing more then you can do it in this way.

Q. And one of the reasons that scientists like yourself give data like optical rotation is to give some additional evidence about stereochemistry, correct?

A. To give additional evidence of experimental data characterizing the enantiomers.

Q. And that data is given so that another scientist elsewhere can try and reproduce what you've published, correct?

A. And apply different methods to prove not only one.

Q. I think you said this during your direct examination but I just want to make it clear, if we just focus on what's printed, 1S 2S, that's not Tapentadol, correct?

A. These are the wrong descriptors describing Tapentadol. That's correct. This is wrong. The descriptor 1S 2S is wrong.

Q. If we add in what has been printed in hand the 1R 2S, this likewise is not Tapentadol?

A. This is also not a correct description of the stereo descriptors.

Q. So just looking at the printed version -- actually Mr. Haw if you can go out and include the structure.

Just looking at the printed version, there is a difference between the chemical nomenclature and the figure that's depicted here, correct?

A. This is correct.

Q. Now, given your specialized experience in stereochemistry, I think it's fair to say that you did pay attention to the stereo descriptors when you reviewed the

application. Is that right?

A. Yes.

Q. And you took action so that if there were any errors, that they would get corrected. Is that right?

A. Yes, but those errors were not detected by me.

Q. And this particular change, you can't recall if you were the one that asked for this particular change to be made?

A. I don't think that I was the person who has done it because initials are not mine which are on the left side. I can't tell you who it was.

Q. Now, you talked a bit about the precursor to Tapentadol.

Do you recall that?

A. I recall that.

Q. I think you had a demonstrative up and I think you referred to it as a compound minus one.

A. This was referring to the minus 41 molecule as a precursor.

Q. Okay. And if we look at that, Mr. Haw, defendant's trial Exhibit 950, it should about lines 31 and 32.

Is this what you are referring to, doctor?

A. No, this is -- I'm referring to the synthetic sequence which was described for the other enantiomer. And to refer to the starting material I was referring to a previous example.

Q. Understood. But when you referred to minus one being

the precursor, is that because of the reference here?

A. This is correct.

Q. Okay. So, if I recall your testimony, your testimony is that compound minus one is correctly named in the patent application, correct?

A. This is correct.

Q. And you used what I think you said was a non stereo selective reagent to react with minus one, correct?

A. No. First the chirality was introduced during the chemical reaction.

Q. Understood. But at the subsquent reactions you used what you referred to as non stereoselective reagents?

A. I wouldn't say this is the wrong term because once you start with defined stereochemistry and you do even a non chiral transformation, this reaction remains elective because the selectivity of the stereo system, the starting molecules are not changed.

Q. Let's me rephrase. You used chemistry that you thought would not change the stereochemistry minus one?

A. Yes.

Q. Okay. And you in fact had experience with similar reactions with minus one that did not change the stereochemistry?

A. Yes, this is correct.

Q. And is it fair to say that that experience led you to

assume that the absolute stereochemistry of the precursor minus one would mimic the absolute stereochemistry of Tapentadol?

A. This is exactly how I have seen it because the stereo centers were not inverted. They were remained as the same based on the method we have applied.

Q. And at your deposition you could not recall exactly in times when you discovered that the chirality of the absolute configuration of Tapentadol did not in fact match that of minus one, correct?

A. This is correct. I can't say any specific date.

Q. But, you do recall that the discovery was after the filing of the patent application?

A. Yes.

Q. And we know that it was after the filing of the patent application because you would have corrected it to be the correct configuration?

A. If I would have detected earlier, I would have corrected it.

Q. Okay. Do you specifically recall, Dr. Buschmann, giving a presentation to fellow scientists in which you described the confusion that existed with regard to the birth of Tapentadol?

A. Yes.

Q. Okay. And you recall exactly what you presented to them?

A. The source of forthcoming posts, the school of medicine and chemistry were some examples, discovery of molecules is represented in a short course. So Ph.D. to Ph.D. students coming from South America.

Q. What is a short course?

A. A short course is a comprehensive course where different topics of medicine and chemistry were presented and also have exercises related to real life, the pharmaceutical research. And this was considered as one example from the industry.

Q. Do you recall precisely what you showed them in terms of the confusion?

A. I wanted to use this example to be as precise as possible whatever they are doing to avoid such situation which I am now asked here in the course --

(Laughter)

Q. Can I show that to you so you can show it to the Court?

MR. SCHULER: Your Honor, may I approach the witness and the bench?

THE COURT: Yes, go ahead.

Q. Okay. Is this the set of material you recall?

A. Yes.

Q. This set of material, it appears to be a presentation you gave at a conference or short course in Rio de Janeiro?

A. Yes.

Q. It was just last year in 2015?
A. January 2015.
Q. And if we could turn to the page, it's about the 76th page. Is this what you -- it's up on the screen if it's easier.
Is this what you recall you presented?
A. Yes.
Q. And it looks like on the right-hand side you have an excerpt from a notebook of your lab. Is that right?
A. Yes, this is right.
Q. And this particular page is from the notebook maintained by the gentleman on the left, Peter Janssen ?
A. No, this was information where the relevant information was taken together to send the compounds from our lab to analytical department. So it was not considered as a copy of a lab quote of Mr. Jansen. This page I have prepared.
Q. Why did you put Mr. Jansen's picture on this page?
A. Because I would give reference that he was a person that was present the first time Tapentadol had applied to synthesize as one of our technicians and the reference that he shortly died afterwards. So this was my intention to honor him as part of this discovery.
Q. So, you prepared the notebook page?
A. This notebook page was prepared by me, yes.
Q. And you circled some information. What did you circle?

A. I circled the wrong thera descriptors which are indicated here.

Q. And in the text you write is it a boy or is it a girl question mark. Do you see that?

A. Yes.

Q. Is it fair to say that when you witnessed the birth of Tapentadol, you thought it was a boy with the SS configuration?

A. No, it was just a joke to entertain the students and to say okay, how important it is to take care of any detail and not to refer what you think is right. Just control it 2, 3, times or more. This was the message.

Q. Okay. If I can distill that a little bit. You are saying don't make assumptions, verify?

A. Try to control whatever you are writing down as much as possible. This was the main message.

Q. Okay. Why did you put the phrase Is it a boy or is it a girl question mark?

A. This was a joke entertaining the students. After two hours' lessons, it was necessary to make some jokes.

Q. After another thirty minutes, I'll try and make a joke.

A. Okay.

(Laughter)

Q. Now, you've transitioned this to a topic I want to talk more about. You can put that up. As to maintaining lab notebooks, you had certain rules for your lab personnel, right?

A. Correct.

Q. One rule you had was that a scientist should record what they did?

A. Yes. And to compile any available information in one place. This was one of the routes I tried to establish that I had started at the lab at this time.

Q. If a scientist saw a particular value on an instrument, they should also record what they saw, correct?

A. To write down any relevant observation.

Q. And I think you said this but the lab notebooks were maintained by the company so that people could go back and refer to what had been done before, correct?

A. This is correct.

Q. All right. Let's look at the notebook pages. I think you talked about these on direct examination but I have only got single pages. So to make it less, if we could put up defendant's trial Exhibit 974.

This is a translation, doctor. If you'd like to look at the original German, it should be 973.

THE COURT: That's fine.

Q. The handwriting, it refers to 322-1-1?

A. That is right.

Q. And you described what that means during your direct examination.

A. Yes.

Q. And there is a compound that you've written out and that is Tapentadol?

A. Now known as Tapentadol, not known at this time.

Q. Fair enough.

A. However, without indicating any stereo centers so it was a constitution of Tapentadol hydrochloride.

Q. With the minus.

A. With the minus which was coming in after measuring the optical rotation.

Q. And then down below there is some optical rotation data down below under processing and purification.

Do you see that?

A. I see it.

Q. Is that the same value that's recorded in the patent application?

A. Minus 27.5 I think it is the same.

Q. And let's go to the page ending in 951. Does this appear to be the page that you excerpted for your short course presentation?

A. Yes, it is.

Q. And here you have again a designation of the stereochemistry, correct?

A. This is correct.

Q. It's 1S 2S, correct?

A. It is assigned as 1S 2S, the structural formula. It's

showing 1R 2R.

Q. 1S 2S is the same as appeared in the original patent application, correct?

A. This is correct.

Q. Now, let's put up defendant's trial exhibit 979. And I think you talked about this. The date here is in April of 1994?

A. This is correct.

Q. And this is batch 01 which means that you were synthesizing it for your colleagues to do some additional work on pharmacology, correct?

A. This is correct.

Q. And here again the structure is designated as SS, correct?

A. This is correct.

Q. Now, let's look at 977. But we may not even need to. You did testify about the NMR confirmation, correct?

A. Right.

Q. And I think you looked at the NMR but I think this is the, if we go to page, the box under the experiments, there was a reference to the hydrogen NMR data.

Do you see that?

A. Yes.

Q. Okay. And is it fair to say that you considered the necessity of hydrogen NMR confirmed the structure's importance

because of the possibility that -- well, let me backup.

You had changed the reaction scheme. That was one of the points you made with Mr. Best on direct examination?

A. We exchanged the sequence of transformation steps, not the synthetic root. As such for a chemist it's not a different group because you are starting with the same precursors following the same fee in terms of molecular structures and just saving and trying to make a better sequence that the steps are converted.

Q. That's my other point. You just changed the sequence of steps, correct?

A. Yes.

Q. But you needed, you considered it helpful or important to have NMR data to confirm the structure because of the possibilities that the reaction conditions would not create your desired compound. Is that true?

A. NMR, hydrogen NMR was considered as one of the methods to have a direct control if you have the same octane in the previous experience or not.

Q. You wanted to confirm that so you could give additional quantities to your colleagues, correct?

A. This is correct.

Q. And if I recall, you specifically wanted confirmation of that because you were concerned a little bit that the contrasting condition of the hydrobromic acid reflux reaction

might destroy another part of the molecule?

A. If you refer to the reaction condition has such a very strong assay in the hydro aromatic ratio on the boiling point conditions, of course you have to think and consider if this may make a change.

Q. And so I think you testified you wanted to change the solvent ratios to make it a little less drastic, correct?

A. No, we changed the sequence to have better conditions to make larger amounts in the same available volume of flasks available in our lab.

Q. And I think you testified earlier that the melting point, that's F.P. here, but that's the melting point?

A. This is correct.

Q. And I think you told the Court that you believed that there's a typo?

A. Yes.

A. If you refer to the first batch, it was melting point was not measurable because there was some residue solvents. And here the second batch it was better to write and it was available. So this melting point giving it independent, I don't know where it's coming from. But it is not the melting point we have measured. And I haven't detected a patent application where this compound has the wrong melting point.

Q. Do you recall I asked you at your deposition why this data does not appear in the patent application?

A. Yes.

Q. Do you recall what your answer was?

A. I have said it's the same because I think because it is how it was. So the melting point was not considered as one of the most important features characterizing a compound. It was depending on the method, how you have measured it, how fast was the heating sequence, and all the things.

So, it was one characteristic of a compound of a batch of a sample.

Q. I was just asking do you recall what answer you gave me at your deposition.

A. I think this was the answer but I am not hundred percent sure.

Q. Do you recall telling me you don't know why the data is not in the patent?

A. I don't know. This is still correct. If I would know, I would have corrected it. And it would be a pleasure for me today where this error was coming from. I don't know.

Q. Now let's look at the change of the designation DTX-952. Do you recall, Dr. Buschmann, that this is -- you can go down a little further.

A. Yes.

Q. That this was the amendment that changed the chemical name? And specifically it's the last one referred to here which is Page 30, Line 29, change 1S 2S to 1R 2S? Do you see

that?

A. Yes.

Q. You recall that was one of the changes that was made in the course of the patent's life?

A. This is correct.

Q. All right. And if we can turn to the next page. And the first paragraph says the foregoing amendments are submitted to correct inadvertent consistencies in the RS stereo descriptions in the chemical names in examples 24 and 25.

Do you see that?

A. I see that.

Q. It says in the next sentence that the supports for the amendments is found in the original formulas in examples 24 and 25.

Do you see that?

A. I see that.

Q. And so the formula that is set forth with regard to example 25 is one that depicts the corrected 1R 2S stereochemistry, correct?

A. Correct.

Q. And Dr. Buschmann, you collectively at Grunenthal thought that the 1R 2S designation was the correct one as of the date of this submission in 1997. Is that correct?

A. This is correct, yes.

Q. Now, I want to go to your declaration which is

defendant's trial Exhibit 1015. You testified about this on your direct examination, correct?

A. Correct.

Q. And I don't know that you testified about the date but can you recall generally that was in 1997?

A. Yes.

Q. Okay. And is it fair to say that you read this declaration, which is only four pages in length, in its entirety before you signed it?

A. Yes.

Q. If we turn to the end of the declaration, the first couple of lines of Paragraph 10 just say you've read it and all the statements are true to the best of your knowledge, correct?

A. This is correct.

Q. All right. Now, if we could turn to Paragraph 8, Mr. Haw.

And in the first sentence of Paragraph 8, doctor, you referred to the analgesic activities of certain compounds. Do you see that?

A. Yes, this is correct.

Q. And the example numbers you give are 18, 1, 20, 16 and 24.

Do you see that?

A. I see that.

Q. And we looked at it earlier, but example 24 is the

enantiomer of Tapentadol, correct?

A. Correct.

Q. That has the opposite configuration, correct?

A. Correct.

Q. Here you talk about threo compounds and then erythro diastereomers.

Do you see that?

A. Yes.

Q. Can you briefly describe for the Court what the threo configuration is versus the erythro?

A. This is another nomenclature system applied for compounds where you have more than one chiral center attached to each other that meets two chiral centers which were attached to each other. And as a consequence you have four stereoisomers. And these four stereoisomers have a certain relationship to each other.

On one hand you have diastereoisomers which have different physical chemical properties. And this diastereoisomer consists of two enantiomeric names that have the same committed properties we have referred to before. But, with the only difference there's optical rotations showing in the different, in the opposite direction.

So, and here it was assigned that threo and erythro were considered a relative stereochemistry of the compounds.

Q. And do you recall the purpose of your data submission

was to compare -- let me backup.

You synthesized both threo and erythro compounds?

A. We synthesized examples belonging to both series, yes.

Q. Do you recall the purpose of the declaration was to compare the activity of the threo compounds to those of the erythro compounds, right?

A. And to demonstrate it. Although the threo compounds were energy active in the animal models we have used.

Q. Do you specifically recall your lawyer telling the Patent Office that the reason that the erythro compounds were unclaimed is that the threo compounds showed superior in that mouse model that you were talking about?

A. In most of the examples we have synthesized there was higher activity of the threo compounds in the use test models. But of course if you really compare analgesic activity, we have to look to more than one model. It was just the first screening model able to identify energy activity.

Q. Sir, why would you have to look at more than one model to make an accurate comparison of that activity?

A. If you, first of all, you would like to look what is the properties of your of compounds. Of course you have to start with one relevant experiment. And this was in our hands the writhing experiment giving evidence of analgesic activity using oral application is detectable.

Q. But why is it your --

A. If you then recall analgesic activity, you have to refer to the model. And this was the only comment I wanted to make, so I wouldn't say analgesic activity of erthro and threo compounds is different. I only wanted to say based on the experiments we have used, that's the majority of the compounds, there was a slight higher activity of the either diastereomers in comparison to the direct configuration of the erythro ones.

Q. Let's look at what your lawyer said. If you can put up defendant's trial Exhibit 952. This is the amendment we looked at earlier.

Do you see that?

A. Yes.

Q. If we could go to Page 2, I'm sorry, let's just go to, you see the bottom there it says Submitted herewith is your declaration.

Do you see the reference to your declaration?

A. Yes.

Q. Okay. And if we can turn to the next page under the Fischer projection. And the statement is that your declaration quote shows that the claimed threo stereoisomers unexpectedly exhibit a stronger analgesic effectiveness compared to the unclaimed corresponding erythro stereoisomers as evidenced by the lower ED50 values of the claimed compounds in the phenylquinone-induced writhing test.

Do you see that?

A. Correct.

Q. And that explains why the erythro compounds were unclaimed and why the threo compounds are claimed, correct?

A. Correct.

Q. Now, let's look at the data if we could go back to DTX 1015 and the table. And let's look at the first one.

I think you testified a little bit about this but on the left is the threo, right?

A. Right.

Q. And on the right is the erythro, correct?

A. This is correct.

Q. Okay. And the very first one for instance the erythro compounds here has an ED 50 value of 30.0 milligrams per kilogram?

A. Correct.

Q. Per os as you testified to before, is the oral administration?

A. Yes.

Q. And then if we look down to -- let me put it this way, to be superior to that value, the ED50 value would have to be lower, correct?

A. Yes.

Q. All right. So let's look at the last threo listed on the next page which is example 25.

What is the value recited there in ED 50?

A. 38.4.
Q. No, for example 25.
A. 31.3.
Q. That's Tapentadol, according to you?
A. This is referring to Tapentadol hydrochloride.
Q. And that's higher than the ED 50 value that we just looked at for the unclaimed erythro compounds, correct?
A. This is correct. However, you have to compare pairs of compound, and this is irrelevant. So you can make only a judgment if you have the similar structures. Since here was to compare, if you have exact needs, the same attachment of the chiral centers and then to compare what is the higher activity, erythro, so that means in this case it's absolutely right. If you have direct comparison, the threo has a higher activity as indicated here with a lower value than the erythro one.
But, the absolute value you can't compare all components and mix with each other. You can only make a judgment if you have the right comparison. And this is exactly what is shown here.
Q. But just to be clear -- and you did not claim the erythro compound that had a value that was too high of 30.3 milligram per kilograms?
A. In comparison and showing the analog, it's threo configuration was the effect of 5 or 6 more in this test model.
Q. Now, you know what statistical significance is,

correct?

A. Sorry.

Q. You know what statistical significance is, correct?

A. Yes, I know as a scientist.

Q. And just for the Court's benefit, statistical significance is a measurement that scientists make to determine whether the observation that is being analyzed is more likely due to random chance or particular effect, correct?

A. This is correct.

Q. And for purposes of the data in this table, you took that data from the people in the pharmacology department, correct?

A. This is correct.

Q. And you did not take into account whether or not the data they gave you was statistically significant. Is that fair?

A. Because the statistical significance was given by the people and by the data coming from the pharmacological department. And that was the reason that always we have controls within. And of course whatever data you are generating in the biological system, we have the statistical variants.

Q. But, that's interesting you say that. Your declaration does not report any statistical analysis, does it?

A. No, this is correct.

Q. And your declaration likewise does not say anything about whether a control was used, correct?

A. This is correct. But it was used. That this data which were coming were done under this consideration because they were done under these circumstances. And whatever additional information was needed to clarify what is the range of the statistical relevance, this was not important.

Because the statistical variance, whatever test you are doing under the same condition, is a compound, isn't the same range. So what we have compared, other important data than this data, were controlled by the pharmacological experts.

Q. Let's go to PTX 1602 which is something you talked about on your direct examination. And I can't remember remember the exact pages, but if could look at the declaration of Dr. Strassberger I think it's at GRT Number 8168.

THE COURT: They are out of order but it's the first page.

MR. SCHULER: It is the first page. Thank you, your Honor.

Q. Are you there, 1602 in your direct examination book?

THE COURT: It's the last exhibit, the first page.

THE WITNESS: Okay.

Q. And you testified about some data sheets. Do you recall that?

A. Yes.

Q. That data does not appear in the patent specification. Can we agree on that?

A. This is correct.

Q. All right. In fact, there's no data of any analgesic activity for Tapentadol example 25 in the data table of the patent, correct?

A. This is correct.

Q. And you didn't mention the Strassburger declaration. Did you read the Strassburger declaration?

A. Yes, I read it.

Q. Okay. If you could turn to the page, Paragraph 9. By the way, let me stop there.

Do you understand the reason that the data sheets were submitted in 2005 was because of the very fact that there's no data for Tapentadol in the patent?

A. This I can't say because at this time I was no longer at Grunenthal.

Q. All right. Paragraph 9, if we look at the third sentence, it says Also, comparison of some of the individual results would not alone provide evidence of superiority of the test compounds.

Do you see that?

A. I see that.

Q. And did you do any data analysis to see whether the data sheets that you talked about show any superiority to the

relevant comparative compounds?

A. Based on examples we have compared, I would say yes.

Q. Did you look at the comparator to BN 200?

A. At this time we were investigating the compounds. And it was not clear if BN 200 was a candidate. So all this data was coming later.

Q. Earlier you said that the comparator that's of relevance is BN 5. Do you remember that? The comparator to erythro.

Do you recall that?

A. First of all, I was not referring to BN 5. Maybe you are referring to BN 4 which was the first linear analog.

Q. I'm sorry, in your declaration do you recall referring to the comparator example to Tapentadol, that's the erythro compound?

A. Yes.

Q. Did you analyze the data sheets that looked at to see whether there was corresponding tests results for the ethryo in the same test models?

A. I was comparing the data which were available and I was trying to set for one experiment to clarify what are the differences in the given test monitor.

Q. In your direct examination you looked at different --

A. Correct.

Q. -- tests?

A. Yes.
Q. Administer amounts. Do you recall that?
A. Yes.
Q. Did you look at the comparator results for the erythro in that same model?
A. It was, this represented results not for every application for all compounds. All data were not available.
Q. Let's look at the other patent which is DTX 304. And this you understand to be the crystal form patent?
A. Yes.
Q. If we could go to column one, the heading brief summary of the invention at Line 46. And if we look at Line 46 it says U.S. patent numbers and it starts with 6,248,737 and that's one of the patents you testified about this morning, correct?
A. This is correct.
Q. As well as 6,344,558. And I'll skip the European one, disclosed the substance and the synthesis of and they say and that's Tapentadol, correct?
A. This is correct.
Q. It says in example 25, correct?
A. This is correct.
Q. All right. Now, the next sentence says As proven by x-ray diffraction the 1R 2R configuration as shown in the drawing of the structure in example 25 is correct although the configuration is reported as minus 1R 2S in U.S. patent

Number 6,248,737. And I'll stop there.

Do you see that?

A. I see that.

Q. And you recognize that there was a contradiction between the structure and the stereochemistry that's designated, correct?

A. This is correct.

Q. And there was a need for empirical testing in the form of extra diffraction to determine which of those was correct?

A. No. This was considered as an additional information because later on contributing and confirming it was the right structure because even in the name you have optical rotation. And if you look to the starting material where the optical, where the optical stereo centers were confirmed. And having this similarity, it's additional confirmation that it is the right stereochemistry.

Q. That's not what it says here, sir. It says as proven, correct?

A. It's additional experiment which is additionally giving confirmation that assignment in the drawings is the correct one.

Q. Okay. Very simply, could we agree that the word you chose for your patent was the word "proven"?

A. I see the word "proven".

Q. Okay. And as a scientist you used that word between

two competing hypotheses which has been established, correct?

A. I wouldn't say this. It seems we have many, many scientific publications where you have additional experiments coming later where it's then considered as proven. But, this doesn't mean this is a single experiment which is made approved.

It was additional information what was considered before. And I know several publications, but this one is used in this sense.

Q. Fair enough. Let's put it this way, the proof you recite here is not the structure of example 25, is it?

A. I don't understand this question. Sorry.

Q. The proof that you refer to in this sentence is not the structure of example 25, is it?

A. No, this is just the proof that the chemical drawing is showing the exact and correct stereochemistry and the formula is the correct one. And here it's confirmed that it's the correct drawing and the correct stereo descriptor was done in the correct way. This is what I'm reading here.

Q. The confirmation is an empirical test called stray light diffraction, correct?

A. This is one method.

Q. Now, there was also a contradiction between the '737 patent and the next one you refer to which is the '558 patent. Do you see that?

A. Yes.

Q. And the '558 patent gave yet a different stereochemistry. It says 1S 2S, correct?

A. Yes.

Q. All right. So we have three competing possibilities. We have the 1R 2r, 1S 2S and we have the structure, correct?

A. No, you have the structure and the only thing is that you have a different descriptor. For experts and the chemists, the structure was a relevant one and this was the correct one.

Q. I find that interesting you say that.

Why did you then report to your fellow colleagues in the field that there was contradictory information in the reports of the stereochemistry?

A. Because this is not stated here. It's just referring that there was a mistake and other R in the designation, the stereo descriptors. And it was additional confirmation using the extra single structure confirming the stereo centers as shown in the drawings. And this was the understanding to write it in this way.

Q. All right. Now, I just want to ask a few more questions by way of background about how this patent came to be.

We're talking about Tapentadol having a crystal structure because it's coming out in solution, correct?

A. If something is coming out as a solid of a solution, it may be crystalline. It may be amorphous. The crystalline structures could differ in the crystallic groups.

Q. Let's look at what you said at your deposition at Page 142, and 142 starting at Line 16 through Line 19.

Do you see that I asked you Okay, and here we're talking about the Tapentadol having a crystal form coming out of a solution, right? And do you see that your answer was right?

A. Because this was a different question. Here you are asking me about Tapentadol. Your last question was in general and this was a refining.

Q. I will refine my question. Can we agree that your patent talks about example 25? We are talking about Tapentadol crystallizing out of a solution?

A. What I stated here is that the powder which was solidified coming out of solution was considered as the crystalline powder.

Q. One of the reasons that led to the work that led to this patent was the fact that regulatory agencies would expect you to know whether Tapentadol was polymorphic, correct?

A. No. There are general guidelines existing where polymorphic forms may have an impact on our dosage forms. And there was a certain guidance in the ICH guidance or industry from the FDA how this polymorph form should be considered in a

development program.

Q. That's what I was getting to. You understood the regulatory agencies would expect you to know as a company whether Tapentadol was polymorphic?

A. This is not correct. If you look to the guidelines, you have to decide if it is important to be considered or not. But it's not expected to do so. It depends on all other information you have of your product. And even for many other compounds which are crystalline and which are allowed to go to market by the FDA polymorphic forms are playing not an important role even as described.

Q. Okay. Let's look again at your deposition Page 144.

A. Yes.

Q. Line 10.

A. Yep.

Q. I asked you, I think the environment you mean is that the regulatory agencies would expect you to know whether it's polymorphic or not.

Do you see that question, sir?

A. Yes, I did.

Q. And you see your answer was, Not only the regulatory bodies, it was important for any further developments that, to have knowledge of solid form characteristics.

Did I read your answer correctly?

A. Yes, but the meaning and the circumstances isn't

exactly the same.

Q. Sir, that was my only question is whether I read it correctly.

A. Yeah, okay.

Q. Now, if we could go back to DTX 304 at the bottom of column one, the last paragraph, the very last sentence says this new form A --

THE COURT: I'm sorry, what document is this?

MR. SCHULER: I'm back at 304 which is the '364 patent.

THE COURT: I have it.

Q. And the last sentence of this column says This new form A, and I'm not going to read the chemical name of Tapentadol, is very stable at ambient conditions and therefore useful for producing a pharmaceutical composition.

Do you see that, doctor?

A. I see this.

Q. And what you're saying here is that we have form A, we have form B, and we know empirically that form A is more stable at ambient conditions. Is that right?

A. Polymorphic validity at least that is two different dimensions. On one hand the thermodynamic stability and the kinetic stability. Given the thermodynamically unstable compound under certain conditions may exist because of kinetic reasons.

Q. I guess more basically I'm asking, that's an empirical statement, correct?

A. This is an empirical statement, yes.

Q. And the way that scientists in your field go about determining empirically whether one form is more thermodynamically stable than the other is to compare their relative solubilities, correct?

A. I wouldn't know. The solubility is not correlated of two polymorphic forms to stability. This would be a surprise. I wouldn't state this statement.

Q. Okay. Let's look at --

A. Different polymorphic forms may have different solubility but solubility is stating not what is stable or less stable.

Q. Sir, isn't it true that if you dissolve a crystal in any solution, that the more stable the polymorph, the more energy it takes to dissolve the crystal?

A. No, because then you have to refer to what suitability conditions you are applying. And this is exactly referring if it is a thermodynamic or kinetic solubility. There is a difference. And this is exactly going to the fact that polymorphic forms in terms of a thermodynamic effects solubility but you can't make a prediction that its a more stable form is less soluble.

Q. I'm not asking about predictions. I'm saying when

scientists go about determining empirically whether A is more stable thermodynamically than B, the experiment they perform is evaluating their solubility in the same medium, correct?

A. They measure solubility if different polymorphic forms are there.

Q. Right. And the one that's more stable will be less soluble in the same medium, correct?

A. This I wouldn't confirm.

Q. Okay. You don't know or you disagree?

A. With my knowledge, with my limited knowledge as a scientist, I wouldn't agree because --

Q. Okay.

A. -- because you have to specify in terms of thermodynamic and kinetic solubility the contingents you are using to measure solubility and this is quite a complex situation. So really you have to specify what you are referring to. And in general this statement from me as a scientist with my limited knowledge is not correct.

Q. Okay. Let's look at DTX 205. Do you see, doctor, this is entitled background information for the October 2002 ACPS meeting. And it has the title scientific considerations of polymorphism in pharmaceutical solids.

Do you see that?

A. Yes.

Q. If we go to the bottom of the page, go to the bottom of

the page on the left-hand side, you see it comes from the FDA website?

A. Huh.

Q. Is that a yes?

A. Yes.

Q. And if we can go to Page 3 under the heading stability and manufacture ability and the second sentence, I think we can agree with right, The most stable polymorphic form of a drug substance is often used, is that consistent with your experience?

A. Yes. I would say yes.

Q. And then the fourth sentence says The relative polymorphic stability may be determined by an iterative examination of the relative apparent solubility of supersaturated solutions of polymorphic pairs.

Do you see that?

A. Yes, but, you know, also what is behind this statement an apparent solubility has completely different mention than just situation solubility. And then the second point is you are talking about supersaturated solutions which is quite a complex thermodynamic system.

Q. I was just going to ask do you agree?

A. There is for me not a contradiction.

Q. And is there any such data in the patent specification in the '364 patent?

A. Apparent solubility and from supersaturated solutions, I am not aware. I can't recall.

Q. Okay. Do you agree that the relative thermodynamic stability of polymorphs is determined by the solubility?

A. I read it, yes.

Q. Just a few more questions, doctor, about the '364 patent. And we can put it back up if you need it. But, I think these are just general questions.

There's a statement in the '364 that following example 25 allegedly results in form B. Do you recall that?

A. Yes.

Q. And to your knowledge that example 25 allegedly generates form B is not something that's based on your personal experience in the laboratory?

A. No, because this investigation conservation was done afterwards.

Q. And let's look at defendant's trial Exhibit 1069. But we are going to use, I'm sorry, we are going to use 2002.

And do you have that individual page?

A. Yes.

Q. This is a translation of an e-mail that you received from Dr. Fischer. Do you see that?

A. I see that.

Q. And that's from January of 2002, correct?

A. This is correct.

Q. And Dr. Fischer writes, I have looked through the following batches once more. In all the on hand clinic batch x-ray powder data, polymorph A is present.

Do you see that?

A. I see what is written there.

Q. And if we look down at the results except for the one for which there was no data, there is modification A listed for each of those batches?

A. This is correct. But, you have also read this information in a different way because what is reported here that center, whatever the history, the center you are investigating showing form A, because since the polymorphic composition was not measured after manufacturing as the specification item, nobody knows what was the real polymorphic composition after manufacturing.

And this sample is referring, that sample taken out of those batches were showing in the moment they were measured form A.

Q. I think what you are saying is when they took samples out of these batches, they found form A at the time that they took the samples.

A. No, because this is not -- I can't say because I don't know at what time the samples were taken, what was the sampling procedure, and how the samples were stored, what happened to the samples.

So, I would say the only thing I can conclude what I am reading here that during the time of measurement samples, whatever was taken out of those batches was showing form A. But, it's not telling me that the batches are form A.

Q. Fair enough. Do you ever recall getting an e-mail from Dr. Fischer saying that each of the clinic batches exhibited form B?

A. There is a shortcut summary. But, what we also have to understand was --

Q. I'm not sure you're answering my question.

Do you recall ever getting a different e-mail from Dr. Fischer in which the report was each of the clinic batches had form B?

A. I can't recall this. If you look to the date 17th of January, this was, the moving company was in front of my door going to Barcelona. So this was the day of course I received this and I put as much effort to contribute to my last date at Grunenthal research. But, this was really out of my, let me say, supervising activities.

Q. Now, I think you told me earlier that Mr. Jansen was the first one that synthesized Tapentadol?

A. This is correct.

Q. He never showed you results indicating that he had synthesized form B. Is that true?

A. No, this was unfortunately not possible because he died

and everything was done much later.

Q. And your co-inventors -- we can put the patent back up. Do you recall your co-inventors were Dr. Fischer, Dr. Gruss and Dr. Lischke?

A. Right.

Q. And none of those individuals were synthetic chemists, correct?

A. This is correct.

Q. And at the time of your deposition, at least you could not recall Dr. Fischer ever showing you results indicating that he had obtained form B of Tapentadol, correct?

A. As far as I could recall, yes.

Q. And at your deposition you could not recall Dr. Gruss ever providing you results where he said that he obtained form B according to example 25, correct?

A. This is correct.

Q. And likewise you do not recall Dr. Lischke providing you results indicating that she had synthesized form B according to example 25?

A. No.

Q. And there was an outfit called SSCI that did some characterization work?

A. This was a company which was decided to make the polymorphic investigation.

Q. And you do not recall SSCI ever indicating that they

obtained form B by repeating example 25 from the earlier patent, correct?

A. This was a process started trying to look for it. So the precise answer, I can't recall.

MR. SCHULER: No further questions, doctor.

THE COURT: Thank you very much. Anyone else on behalf of the defendants?

MR. ALY: Yes. I don't want to pass up an opportunity.

THE COURT: How long do you think your examination is going to take?

MR. ALY: Forty minutes.

THE COURT: We are going to take a break.

(Whereupon a short recess was taken.)

THE COURT: All right. Let's continue with cross examination.

MR. ALY: May it please the Court.

THE COURT: Did you look at the new exhibits?

MR. BEST: We did and mostly it's fine. We think we have one objection though to one of the translations again and to defendant's Exhibit 1062. We would ask Dr. Buschmann also have in hand PTX 1486.

THE COURT: I'm sorry, I couldn't hear. What is the problem with them?

MR. BEST: The problem is that there's sort of a

complete discrepancy between the translation of one sentence.

THE COURT: Just talk into the microphone.

MR. BEST: There's a complete discrepancy in the translation of one sentence which reads on the one hand that something was critical and on the other hand that it was not critical effectively.

THE COURT: So how do we suggest handling this? Do you have two separate translations? Is that what you are thinking of doing, submitting two separate translations?

MR. BEST: I think that's right.

MR. ALY: If that becomes an issue, the witness can have both and we can talk about it from that point forward.

THE COURT: That's fine. Are you both good with that?

MR. BEST: Yes.

THE COURT: So, we will have both used. Any other issues with respect to the exhibits or the demonstratives?

MR. BEST: I think not.

THE COURT: That's it? Okay.

MR. BEST: May I approach, your Honor?

THE COURT: Yes, please. This is plaintiff's version?

MR. BEST: Correct.

THE COURT: What is the number on your version?

MR. BEST: PTX 1486.

THE COURT: What is number on defendant's version? Mr. Aly, what's the number on your translation? Plaintiff's is 1486 and yours is what?

MR. ALY: He was the one that was looking at both so let me just find out actually.

THE COURT: I just want to have it in my notes.

MR. ALY: 1062.

THE COURT: Thank you. All right. Any other issues with respect to exhibits or demonstratives? Anything? No. Go ahead.

MR. ALY: Thank you very much, your Honor.

THE COURT: Thank you.

CROSS EXAMINATION BY MR. ALY:

Q. Dr. Buschmann, good afternoon.

A. Hello.

Q. You are an inventor named on the '593 patent. That's the reissued compound you understand that, correct?

A. This is correct.

Q. You're a named inventor also on the '364 patent, that's the polymorph patent, correct?

A. This is correct as well.

Q. And the third patent method of use, neuropathic pain, you are not named as an inventor on that patent?

A. This is correct.

Q. Now, as a matter of timing, when the '593 patent, the original application was submitted to the Patent Office, you worked at Grunenthal at that time, correct?

A. This is correct.

Q. And as a matter of timing when the '364 patent, what became that, the application was submitted to the Patent Office, you were no longer at Grunenthal, correct?

A. This is correct.

Q. Now, in terms of the '593 patent, there is an example in example 25. You are familiar with that?

A. Yes.

Q. I'd like to look at that together with you. It's DTX 920, column 19. And example 25 its start above the picture and goes to right there.

And Dr. Buschmann, example 25 from the '593 patent, that's what we see on the screen here. It has an image of a compound, correct?

A. This is correct.

Q. And you recognize that compound to be Tapentadol?

A. That is correct, Tapentadol hydrochloride.

Q. Tapentadol hydrochloride. Thank you. The process for getting to Tapentadol hydrochloride as shown in example 25 is they are starting with an enantiomer minus 21. Is that correct?

A. This is correct.

Q. And that's the Tapentadol that's provided, that's the result, and the starting material for that is you look at example 24 to see how to get to that material at the end of it, correct?

A. This is correct.

Q. Now, let's look at example 24 then so that we can talk through that proceeding. It's on column 17 is where it starts on the bottom left. Example 24 has instructions for making it. It calls it a plus 21 as you see on the top picture here right under the heading example 24. Is that correct?

A. This is correct.

Q. And that's because that's another enantiomer of the precursor used to make the Tapentadol minus 21, correct?

A. If you are referring now to the series it is a precursor giving the other enantiomer of the hydrochloride.

Q. And to get to the other enantiomer Tapentadol hydrochloride, there are three steps provided in example 24. There's a first step, a second step and a third step outlined in the patent, correct?

A. That is correct.

Q. I want to look at the third step which is on column 18 starting at Line 61 and going to column 19, Line 11.

Now, if we want to make a crystalline Tapentadol hydrochloride, this procedure the third step shows us how to do that with using the minus precursor, correct?

A. This is correct.

Q. And you see in the third step here how it starts with 4.3 grams of plus 23, right?

A. Right.

Q. Plus 23 is a precursor that then goes through some steps in this what's called third step, correct?

A. Correct.

Q. Now that precursor plus 23 is added to a hundred milliliter of concentrated hydrobromic acid, correct?

A. This is correct.

Q. Let's go to the next part of this. In fact, let's just, let's do that.

Now, if you look at this, the procedure, the recipe here is you start with that plus 23 which is a solid, correct?

A. Yes.

Q. And then you put it into a solution with other ingredients and reactants, correct?

A. It was dissolved in concentrated hydrobromic acid.

Q. When it's dissolved there is no more solid, no more crystal. It's solution?

A. This is solution. This is correct.

Q. There are other steps that are done in the procedure or the recipe, so to speak. And another compound comes out as a result of the process that's shown here, correct?

A. This is correct.

Q. Now, to make sure that you're starting with the correct starting components here would be plus 23 for Tapentadol, it would be minus 23, there are tests to make sure that that's the correct starting compound, correct?

A. This is correct.

Q. And NMR would be one such test?

A. NMR is one of the possibilities.

Q. And you have that starting compound. Now the procedure goes to this after extracting twice. I want to show that part. It's with 50-milliliters of the dichloromethane in each case, correct?

A. That's correct.

Q. You are supposed to put it through 50-milliliter of dichloromethane two different times, correct?

A. Correct.

Q. Now right above this is there's a treatment with the concentrated sodium hydrogen carbonate solution until a alkaline reaction is obtained. Do you see that?

A. Yes.

Q. Alkaline means a ph which is above 7, 8 for example, correct?

A. This is correct.

Q. Now, if now look at dichloromethane, that's the step that's next to the last sentence, it's distilled off under vacuum and then the residue is taken up, correct?

A. This is correct.

Q. And there's a measurement for that. Four grams was found there?

A. Yes.

Q. And there's an addition of this trimethyl chlorcyine (ph) and water, correct?

A. Correct.

Q. And then the result of that is the hydrochloride salt is crystallized out, correct?

A. This is correct.

Q. And in this example 3.8 grams was the result, correct?

A. Correct.

Q. These are all for this example 24 measured values. Is that correct?

A. This is correct.

Q. Now, if we go to example 25, still on the same screen here, the bottom half, yes, from there down, the steps here, we also have some specific steps to the recipe. We have here we start with the minus 23 compound and go through the other procedures that were explained in the third step of the prior example, correct?

A. Yeah. It's referred to the starting materials minus one, following the steps which are then exemplified in example 24.

Q. There's a melting point, specifically given, of 168 to

70 degrees celsius, correct?

A. This is correct.

Q. And the alpha, this is the rotation angle that's measured is 27.5, correct?

A. Correct.

Q. And the conditions in which that was measured is there's C equals .97. It's a grade of methane, correct?

A. This is correct. And specific concentrations one per hundred millimeter which is not normally assigned at this value.

Q. I understand. And, Dr. Buschmann, the reason I'm walking through this with you is to lead to this very important question. Did you ever follow these steps shown in example 25 and 24 to make Tapentadol hydrochloride?

A. Yes.

Q. Are you sure?

A. I'm very sure because I have done it.

Q. Now, when you did the work, you testified on direct examination of making what you called batch 0, correct?

A. This is correct.

Q. You testified on direct about making batch one, correct?

A. This is correct.

Q. You did not testify about synthesizing any other batches of Tapentadol hydrochloride, correct?

A. This is correct.

Q. So, when we're looking at those two batches, you would expect that the numbers you recorded for the data would match the numbers reported in the patent. Isn't that true?

A. Can you rephrase the question?

Q. You would expect -- yes, of course.

Dr. Buschmann, if you had done the test that's shown in example 25, you would expect that the numbers reported in the notebook would match the numbers reported in the patent for the different steps in the procedure, correct?

A. Yes.

Q. And have you until now done that comparison to confirm that, in fact, the procedure and numbers that were in your notebook was transferred to the patent correctly?

A. I haven't detected the transcription error which arise in light of the melting point. So I am somehow lost with these questions.

Q. Which of the batches, batch 0 or batch one or both do you believe, sir, match up to the information reported in example 25?

A. Looking at what we explained in the morning, the sequence are both batch 0 and batch 1 were residing in Tapentadol hydrochloride. The only difference was that the synthetic sequence was changed, which I explained was the result of having large amounts available.

Q. So, you are telling me that in the direct examination you provided two different procedures and said both result in Tapentadol hydrochloride? Do I understand you correctly?

A. Yes.

Q. My question is different. Did you explain a specific procedure -- which one, batch 0 or batch one follow specifically what's shown in the example 24 and 25, or both?

A. It's referred to example 24 and the steps given in 24 were applied for the other enantiomeric series. This is what is written here.

Q. I'm sorry, I am not being clear. Let me try again.

MR. ALY: May I move to here, your Honor?

THE COURT: Yes, absolutely. Is there an exhibit in my book for this? Is this 920?

MR. ALY: Patent 920. It might have a plaintiff number in the materials.

THE COURT: What is the corresponding number for this because I like to write on these.

MR. BEST: If you look at the direct examination binder, it should be 312.

MR. ALY: Plaintiff's 312.

THE COURT: All right. Hold on one second. I'm sorry, what is the Bates number on the bottom?

MR. ALY: Just a moment, your Honor.

MR. BEST: I think you can look at the Bates

number ending 9604 that the page that has columns 17 and 18 and the rest follows.

MR. ALY: 9605 is the one we were just looking at.

THE COURT: I have it. Thank you.

MR. ALY: Thank you. May I proceed?

THE COURT: Yes.

Q. Dr. Buschmann, my question is for the recipe that's shown in examples 24 and 25, is it batch 0 or batch one that you believe follows the recipe?

A. What is summarized here following the example 24 it was the procedure used in the batch one we have synthesized. That meets the cleavage of the methyl agent group that was the last step to reduce the agents in hydrochloride.

Q. We will get to the distinction. But, right now I want to confirm with you.

Do you agree, sir, that batch 0 does not match the protocol in the '593 patent?

A. This is correct because the sequence was different from batch 0.

Q. Looking at batch one, Dr. Buschmann, you explained on direct examination in slide demonstrative slide Number 1, which we can keep this on the left, and Mr. Haw, let's put up demonstrative Number 4 on the right, Dr. Buschmann for the synthesis of batch what we are calling batch Number 1 that's

displayed in your demonstrative slide Number 4 here and that's shown on the screen on the right side, correct?

A. This is correct.

Q. That's the procedure that you believe tracks the procedure in the '593 patent, correct?

A. This is correct.

Q. And the step that you were talking about that makes it different than batch Number 0 is which of these steps that's here?

A. This is the sequence where the milliliter group was cleaved. So, in the batch 0, the phenyl, that means the aromatic hydroxyl group was present. And this compound with the chloride was reduced using simple hydrates as a reducing agent. As a consequence, the symmetry, you have to apply with simple hydrates is two equivalents.

Q. To be clear, in terms of the synthesis of what you are calling batch Number 1 is BU 351, this is the precursor that then is used in the third step of the patent to get to Tapentadol hydrochloride, correct?

A. This is correct.

Q. And that BU 351, so that we can remember it later when submitting materials, is the same as the minus 23 actually, but the minus 23 from the third step of the protocol, correct?

A. Correct.

Q. Now, you did not use that procedure in the process for

making batch Number 0, correct?

A. Correct.

Q. You used a different precursor instead of BU 351?

A. The inter cleavage was done as a different precursor.

Q. Let's look at DTX 977 on the right side, keeping the process on the left, please.

And Dr. Buschmann, this is the last notebook entry relating to batch one, correct?

A. Right.

Q. And this is an English translation. The German should be there as Exhibit 976.

And the question to you is this work that's shown here, is that your work or somebody in your lab?

A. This is indicated with my technician Mr. Jansen who was then responsible person to run this reaction. But, what was normally at this stage in the lab, you have done it together. I was present. So, it was the normal work to work together for a synthetic passage which of course having responsibilities who is the main, let me say, responsible person to run it. So this experiment was done by Mr. Jansen.

Q. And, Dr. Buschmann, you see on the lab notebook page that's DTX 977, the starting material is 5.8 grams. Is that correct?

A. This is correct.

Q. And you can just highlight. And then the experiment

reaction conditions we are to add, this is the sodium hydrogen carbonate, correct?

A. Yes. This is the shortcut summary of this longer procedure which is noted here.

Q. Then what we're supposed to do is add this water and TMCS together combined, correct? That was what the lab notebook said. It was combined or done separately?

A. This was the normal procedure how to generate hydrochloride through the system. So, if once you have the free base solved, you can first apply the three mess or chlorathinine (ph) then the agent of water, or the other way around. Because you shouldn't do it together. But it means that it is plus in vitro generation of hydrochloric acid gas.

Q. My question to you is did you do it one at a time here? Was it done one at a time or was it done together?

A. It was done, depending on the procedure, what is first normally it was done first to give they methyl chlorathinane and immediately water. Because once it's dissolved, so whatever is reaching then from the flask, it depends how fast you are.

Q. Dr. Buschmann, then you see here the rotation is reported for end product, that's the optical rotation for enantiomer Tapentadol hydrochloride as opposed to the plus side of the Tapentadol hydrochloride molecule, right?

A. This is a measure of optical rotation that is obtained

following this procedure and having at a certain time taking a sample and in this report with this measurement, yeah.

Q. That's 26.0 degrees was reported in the notebook, correct?

A. Yes.

Q. Is the .98 in German there but it's C .98 and I think translated as approximately, but it's the C grade of the .98, correct?

A. Then I have to see the original one.

Q. Okay. But you agree that's the reporting method that was used here for that measurement?

A. Yes.

Q. Then the melting point that's reported here, 199.9 to 200.9, correct?

A. This is correct.

MR. ALY: Your Honor, if I may approach the board.

THE COURT: Yes. Go ahead.

Q. Can you see me over here when I'm doing the comparisons?

THE COURT: If you need to get up, you can get up. You can talk into the microphone out there if you'd like.

MR. ALY: I will be loud and he will be speaking into the microphone.

THE COURT: There's one right behind you. If you want to pull it near you, you can do that.

Q. And what you see on the --

MR. ALY: I'm having trouble seeing from here so maybe if you don't mind, your Honor, I will just speak from here.

THE COURT: Whatever's good for you.

Q. I know Mr. Schuler pointed out the melting point difference that's reported in the lab notebook versus what's reported in the patent.

Do you recall that testimony?

A. Yes.

Q. You said that is a typo, correct?

A. Correct.

Q. But here we have the optical rotation in the lab notebook for batch one is minus 26 and the optical rotation in the patent is 27, minus 27.5, correct?

A. Yes.

Q. Here in the lab notebook the methanol condition is .98. Here it's .97, correct?

A. Correct.

Q. Over here you're adding the sodium hydrogen carbonate putting in 5.6 grams. Over here you're supposed to make it alkaline. That's what it says earlier in the step rise procedure, correct?

A. Yes.

Q. Over here the initial starting weight was 5.8 grams of

the precursor. Under the third step it's 4.3 grams of precursor, correct?

A. Correct.

Q. And so what I want to make sure is do you believe all of these are typos, Dr. Buschmann, or in fact it refers to different work that's not really batch one?

A. This is a compilation of all information which were available. So it's not the 1 to 1 copy because even if you measure the optical rotation, you can do it once so the direction is ready or later on before you are giving it to analytical department. Even looking through the concentration you can have different values for optical rotation. It depends on many factors.

Q. I think you can return to your seat if that's all right with your Honor.

THE COURT: Yes, go back. You can have a seat, sir. Thank you.

Q. Dr. Buschmann, I believe what I heard you say is that optical rotation, for example, could be done differently in different conditions. And it doesn't have to always match up. Is that what you are saying?

A. Yes, because it has a variation depending on all the answers measuring the optic rotation.

Q. So, on direct examination you didn't identify any result that had this .97 methanol and minus 27.5 rotation, did

you?

A. I can't tell you because this is a value I measured. Maybe some other documents which referring to that data are not collected. Because it was also an in vitro measurement. That means it was used to secure that and then it was a printout of the demo paper.

Q. I do want to ask you this question. Is it you, sir, personally who took this lab notebook DTX 977 and gave it to somebody else to put into the patent or did somebody else do that?

A. We put all information related to the inventive procedure together and the patent was draft by a different person. This was at this time the rule at Grunenthal.

Q. So when we're looking at procedures, that is the patent that's described as you see it right there on the screen, the third step going through example 25, that's the not something you wrote?

A. This was based on the information we gave to the person which were drafting the application.

Q. Sir, is it something you wrote?

A. I have not drafted a patent application.

Q. Do you know who did?

A. This was at this time quite complex at Grunenthal so different people were involved.

Q. Do you know who did?

A. I can't tell you who it was. I can only tell you at this time it was quite a complicated process making the so called invention disclosure and to transfer the invention disclosure to a patent application.

Q. And is it fair to say since you don't know who wrote the part of the patents we are looking at on the screen example 24 and 25, you don't know what information they relied upon when writing that, correct?

A. I can only tell you what information was provided. And this was a compilation of all data we had at this point.

Q. Let me ask, in the direct examination you went through batch 0 and batch one and I asked you about that was the information you provided today.

A. Yes.

Q. And you provided in the litigation, correct?

A. Yes. Did you provide to the person who was writing the examples 24 and 25 any other documents that you did not provide to us?

A. This I can't recall because it was in '94. And the best method with all compilation of all notebooks coming from different sources was put together. This was the way how it was done. And if you referred to the number of compounds, it's just if you make 4.3 or 5.6 is the only adjustment for making the plausible experiment. So for a chemist there is nothing at all to be concerned.

Q. To be clear, though, Dr. Buschmann, you are not saying all of these things in the patent are typos. You are now saying what's in the patent was compiled from different sources. Do I understand correctly?

A. This may be the reason, yes.

Q. And sitting here today you can't identify -- we're in trial right now. You can't identify pages the materials come from that's reported in the patent?

A. No.

Q. Is that right?

A. Because the procedure is plausible and it is based on what is written there. So that means for a chemist taking the lab notebooks there is no doubt at all that what is given in the lab notebook, it's really the truth consistent with what is written there.

Q. Let me ask you then, Dr. Buschmann, is it possible, is it possible somebody could follow the recipe that's given in the patent and get a different polymorphic form than the procedure in the lab notebook on the right?

A. Because the procedure is one thing and a polymorphic form on the last step is relevant whatever the source of material because it's identical and the polymorph are the subsequent crystallization process which is relevant for getting the polymorph or defined crystalline form.

Q. When you are referring to the intermediate that's used

for the crystallization step here, that's plus 23 for the third step, correct?

A. The intermediate is a free base of the relevant model period. It's not intermediate.

Q. But that's the precursor you are talking about that you put into the solution?

A. Put the free base to salt form.

Q. Your testimony is as long as you have the right starting material, that plus 23 or minus 23 in the case of Tapentadol, example 25, that's all that matters to get the right crystal, correct?

A. If you use the procedure to crystallize it, how it is written --

Q. And when you say the procedure, how it is written, you are referring to the third step portion of the procedure, correct?

A. Correct.

Q. And when you follow that procedure, my question is is it possible that because of the differences in the ingredients used, the person following the patent specification could get a different result in polymorphic form than the person following the lab notebook? Is it possible?

A. No, in my mind it wouldn't be possible.

Q. Wouldn't be?

A. Possible.

A. Because you are following the same exact procedure with the same qualifications and the same information as the compounds. And if you follow this procedures even just to exchange a different step, it shouldn't result in a different product.

Q. But, Dr. Buschmann, let me ask you this important question, you don't have any data that's actually following each of the steps in the patent itself with those amounts and in the order in the patent, correct?

A. The sequence it is written there. I have no doubt why it should be wrong.

Q. I didn't ask about the sequence.

A. Okay.

Q. I'm just asking you do you have any one test which start to finish has this third step procedure done with the right amount of starting material, the right conditions that are in the third step and the right reported melting points and rotation? Do you have that data?

A. The data confirming what was done there or the data to characterize the precursor you are naming?

Q. I am right now following the data that somebody's showing to somebody following the procedure in the data.

Do you have a single lab note or protocol where somebody at Grunenthal followed the recipe exactly as is written in the third step of the example?

A. That's not done in my lab because we are following a procedure at this time not know what polymorph is existing to create from a free base which is in all a solid which were able to be handled. This is exactly what's written there.

Q. Let me direct your attention -- thank you.

Sir, let me direct your attention to demonstrative slide Number 4. Here again is your general procedure, correct, for batch one?

A. Correct.

Q. And what you're referring to in, and what I want to start with here, by the way, is in the synthesis of batch one when you are doing these precursors or steps, the thing that you are saying that really matters to make sure you get the right crystal is whether this BU 351 is the right starting material, correct?

A. This is the right starting material to obtain a compound. This is stereochemistry and the constitution which is 322. Because this is the precursor. This is not saying that it should result in the same crystalline form because no conditions are shown here on the slide.

Q. And on this slide for BU 351 that's there, did you say on direct examination anything to explain that that precursor in your lab notebook was tested to make sure that it was the right precursor?

A. Of course because for this compound which was used as a

precursor also is related and recorded in that notebook for example NMR for this exactly batch.

Q. The NMR you are talking, sir, was it not the end result, the Tapentadol hydrochloride 322-2-1?

A. Not, but, this all the knowledge that we had gained from the precursor 351 was also --

Q. Right. And that's what I'm asking, did you talk about today this NMR data BU 351.

A. That is normally done in the lab. And of course I considered it was correct, otherwise we haven't used it as starting material. This was the kind of in process control we have used going through the different steps which was quite normal at this time.

Q. Sir, did you present evidence today that the BU 351 was the correct starting material for when you made batch one?

A. Yes.

Q. You believe you did?

A. Yes.

Q. All right. And that's referring to the lab notebooks that you talked about where you're testing and showing the BU 322-2-1 result, correct?

A. Right.

Q. Let's look at the analytical information that you reviewed. That will be shown on PTX 345. I believe it was used during the direct examination. And then we are looking at

the production Number 18953 GRT NUC 18953. That's a different page. Go to the next one, DTX 1438. And I will come back to that in moment.

DTX 1248, that's a document that was submitted and sent for analytical review, correct?

A. It was in 2007. I left Grunenthal in 2002.

Q. And so my question is after 2002 you don't know what happened to any of the products that you made while you were in the Grunenthal, correct?

A. I was employed at a different company.

Q. Now batch 0 and batch one, when you left the company, you left batch 0 and batch one at Grunenthal somewhere, correct?

A. This I can't state. I left everything which was under Grunenthal properties.

Q. But, do you specifically remember where you left batch 0 and batch one samples when you left Grunenthal in 2002?

A. No, because compounds which were collected there was standard operation procedure that the demand of compounds was given to a particular department from analytical department. It was eventually given to the pharmacological department. There was then a different compound distribution system but out of any control of chemistry.

Q. And in terms of the compound batch 0 and batch one, do you know where you left them when you left Grunenthal?

A. No.

Q. And did you have a standard procedure to leave compounds that you made in a cabinet somewhere?

A. No, because this was independently done at different labs. How we were doing it normally we are trying to keep a sample as a reference for thin layer chromatography or for reasons. But if a compound was investigated in more detail, any milligram of the compound was needed.

Q. Did you hand the batch 0 and batch one, physical samples to anybody when you left the company, Grunenthal?

A. No, we had done it before because I physically handed over the wire containing the batches O and one to a particular department.

Q. To whom in the analytical department did you hand those vials?

A. That is given to the analytical department where it is used by different people. So there were boxes where you were entering samples.

Q. Do you know the name of a person who you handed it to?

A. One of the experts in the analytical department was Mr. Al Baha (ph) who was checking purity and identity of the compounds.

Q. Do you remember giving batch one and batch two to someone?

A. No, giving it to the analytical department was normal,

having a box, you fill the bottle, the vials and corresponding information on the page. This was the procedure. And this was standard from everybody at this time.

Q. Sir, it might be helpful for me to explain why I'm asking. I want to make sure that the batch 0 and batch one was treated properly and where it went. And I want to make sure, did you hand it to a person or do you just remember giving it to somebody or leaving it with the analytical department generally?

A. No, because everything was given to the analytical department but not to a specific person. But following the specific procedure which was done at the time at Grunenthal.

Q. I understand, Dr. Buschmann.

Have you personally studied the polymorphs that result from different procedures that can be used to make crystals of Tapentadol hydrochloride?

A. No, because I haven't done.

Q. This is somebody else? Dr. Gruss did that, correct?

A. He was involved in this process, yes.

Q. In fact, as you testified on direct examination, you were involved in the hiring of Dr. Gruss to help with that project?

A. This is correct.

Q. Now, in terms of what Tapentadol hydrochloride, in particular what might play a role in whether form A results or

form B results, did you realize that impurities could make a difference?

A. No. This was never observed. Impurities shouldn't have an influence because first of all you have to know what type of impurities you are referring to. And what amount is available. And this both information, then you can ask if this type of impurities in this amount may have an effect on the crystalline form. And what is none today, if you have a different compound present, maybe some crystals will form. But this doesn't mean that other polymorphic form is not formed.

So, it really, this all of this specifically I wouldn't say if you have a standard purity and standard purity was normally referred to in NMR hydrogen, NMR pure, that means greater than 99, 98 percent, the detection limit of this method and within all this, impurities shouldn't have any effect on the crystalline form following the crystallization procedure.

Q. Sir, you personally, in fact, never even thought about impurities possibly having an effect on whether form A or form B results?

A. I haven't done it at this time and I wouldn't do it today.

Q. And you didn't think anyone at Grunenthal had thought of the effect of the impurities on whether one gets form A?

A. Because I can't tell you because I was leaving Grunenthal again in January 2002.

Q. Let's look at DTX 1062. And Dr. Buschmann, this is the exhibit which also your Counsel had provided a different translation in case that comes up. I don't think it will.

A. Right.

Q. DTX 1062 page one, do you see the top right, this protocol note dated September 27, 2001?

A. Right.

Q. Top left participants, you are at the meeting on that date, correct?

A. This is correct.

Q. And the topic of the meeting was status of polymorphism research, correct?

A. Yes.

Q. The research meeting was to update on the work that SSCI had done?

A. Correct.

Q. And SSCI is a company that people can hire to determine what polymorphs are there in their samples, correct?

A. This is correct.

Q. SSCI can also vary the parameters of the making of a polymorph in what's called the polymorph screen, correct?

A. You could summaries it in this way.

Q. Polymorph screening is testing different variables that are known variables to a compound and then seeing what the polymorphs are formed there, correct?

A. No, I wouldn't say this is correct because you are referring to known procedures. And it's quite difficult to have specified methods based on the knowledge of the product properties. And so a known procedure is to have to apply different conditions. But selection of conditions should be based on information which is available.

Q. As far as selection of the conditions used to create the polymorphs, do you know if SSCI did anything special or non routine when they were doing the polymorph screen?

A. Based on my first visit at SSCI, we in depth discussed base physical chemical properties of Tapentadol and how to bring the free base using different procedures to a solid was discussed.

So there was an input of proprietary information which was regarding SSCI who designed the screen test stage in the polymorph screen.

Q. What I want to show you now is the text on this. So were you involved in the meeting?

A. I was involved in the meeting.

Q. Let's look at the paragraph here, the polymorphism screen paragraph Mr. Haw I'm going to be reading form this partial portion right there.

The sentence in the report 1062 says The CG5503 material produced so far at Grunenthal raw material corresponds to the type A which is a thermodynamically stable polymorph at

room temperature and atmospheric pressure. Do you see that?

A. I see that.

Q. CG5503 of course that's Tapentadol, correct?

A. This was another coding system used at Grunenthal.

Q. And SSCI further reports that everything that they have received so far from what they know and from meeting with you people at Grunenthal corresponds to type A, correct?

A. Well, it just --

Q. That's what they are saying, correct?

A. I think this is our meeting minutes. And this is a summary that the samples they have measured were referring to type A. This is what I'm reading here.

Q. And the date of this again was September 2001, correct?

A. This is dated from September 2001, yes.

Q. And I want to turn now in this document to Page 12, DTX 1062, Page 12. Experiments that SSCI did showed that one could make form A into form B doing different things and sometimes was spontaneous, sometimes was using different testing conditions, correct?

A. What is shown here is the kind of cartoon to understand what is very over simplification how to convert from form A and form B. So this is not based on a thermodynamics chromatograph. It's known for discussing something that was thrown on the table. That was the intention of this slide. Nothing more.

Q. When I asked you about impurities, what I want to make sure, at the meeting you attended in September of 2001, SSCI presented that quote, It might be due to impurities which inhibit the transformation from form B to form A, correct?

A. This is correct. And this was discussed. And I rejected this discussion because at this time I was considering this as nonsense.

Q. But, sir, earlier you told me, did you not, that no one at Grunenthal had had this discussion?

A. Look, this was done in 2001 and the impurities was never a topic to be discussed.

Q. Earlier you told me that no one had discussed impurities. Is that correct?

A. You are referring to impurities.

Q. Can you answer my question?

A. Yes. But let me also the chance to explain because you are trying that I say different things and I haven't said different things. Because impurities in terms of attendance, what does it mean impurities? It is impurities in 51 or whatever percent or other items related to the type of impurities.

Q. You didn't qualify your answer earlier did you at all?

A. Okay.

Q. When you were talking when I asked about impurities, you didn't qualify. And you said it depends on which kinds of

impurities. You told me no one talked about impurities.

A. But if it's important issues, it should also be specified. Otherwise it doesn't make sense to put this impurities issue.

Q. Is that a yes you agree with me, sir?

A. I think I will say yes.

Q. Can we look at DTX Exhibit 752? Now this is the '737 patent now which ties to the '593 patent because the '593 is the reissue of this, correct?

A. Correct.

Q. Now, I know we talked about the polymorphic forms. But in the '737 patent, there's no polymorphs actually disclosed, only procedures for making Tapentadol hydrochloride, right?

A. This is correct.

Q. Now in the '737 patent that was filed, if you can, June of 1995, and there's a foreign application July of 1994, correct?

A. Correct.

Q. Now, at that time, sir, as you testified on direct, there were hundreds of compounds in consideration at Grunenthal, correct?

A. Hundreds of compounds were synthesized and tested but of course the testing method was different and the scope of testing.

Q. At that time, this is 1994, 1995, Grunenthal had not

selected or honed into Tapentadol hydrochloride in particular as a compound to develop further, correct?

A. Based on the resynthesis and the example that was given, there was already indication that Grunenthal was interested to investigate this compound in more detail. And exactly this procedure is given which allows you to synthesize the Tapentadol hydrochloride the microgram scale.

Q. Let's go to the claims.

THE COURT: Hold on one second. Where is this in the exhibit books.

MR. ALY: It would be Alkem's binder DTX 752.

THE COURT: What is it in plaintiff's binder?

MR. BEST: I believe it is PTX 668.

THE COURT: Thank you.

MR. ALY: Thank you, your Honor. 668, that is the one in plaintiff's notebook.

Q. And the question I have for you, if we can turn to the claims, and the claims are going to be the last page production number JN NUCENTA 58141, Dr. Buschmann, claim 8 is the last claim in the '737 patent. Is that correct?

A. Yes, that is correct.

Q. And at that time there were only 8 claims that Grunenthal had applied for and obtained, correct?

A. Correct.

Q. And in claim 8 that is what's called a genus claim,

meaning that there's structure backbone but then a lot of groups to choose from for substitution. Is that correct?

A. This is correct.

Q. And under the claim, under the scope of that claim, thousands if not millions of compounds could be included.

Is that correct?

A. Which is normally done using the general formula when looking through the specification of the different substitutions there are already quite narrowed.

Q. Now, let's look at plaintiff's trial Exhibit 537_T. This is one that was from direct examination.

In this document it's from 1995, February 1995, correct? And you testified about this document on direct examination?

A. Correct.

Q. And this is the record of the result of the working group candidate selection, correct?

A. Correct.

Q. And it's in 1995 that there is still yet a list of compounds, if we can go back to the text of the document, and it says After extensive processing, that paragraph, and it says After extensive processing of the agreed upon investigation program concerning the candidate substances, and there are about 8 or 9 substances that are listed here, correct?

A. Correct.

Q. And Tapentadol is one of those, correct?
A. Correct.
Q. So even as of February 1995, there are still several different candidates in play, if you will. Is that correct?
A. Of course we were continuing investigating different compounds as different models which is normal in the pharmaceutical industry.
Q. And DTX 943, then now we are back to the application for the reissue. DTX 943 is the application for the reissue. And on this I would like to advance to Page 14. And in this application for the reissue, we can look at the portion here, The applicants respectfully submit that there are amendments that are made to the specification that relate back to the original patent that was filed, correct?
A. Correct.
Q. And there's text in the different columns that's provided here that were changes that were made. And the statements made to the Patent Office is that we should get credit for the earlier filing date for those changes, correct?
A. Right.
Q. And it is in this application that new claims were added specifically for Tapentadol. Is that right?
A. I have to read it.
Q. Then the '593 reissued patent in this case, again let's go to DTX 920. Let's go to DTX 920.

Now if you look here to the claim, if you look at claim 117 which is on column 138, claim 117, that's the italicized claim added in the reissue. That's one of many claims added in the reissue. And that's specifically to Tapentadol hydrochloride, right?

A. Right, one of others.

Q. Now, I'd like to carry forward with the next patent briefly and that's the '364 patent, DTX 304.

In DTX 304 you are named inventor on this patent as well. Is that right?

A. This is right.

Q. Let's go to column five, example two. And example two is the title of it is preparation of form A, correct?

A. This is correct.

Q. And in the preparation of form A, the statement is given that the starting material for this test was the result of example 25 of European patent EP 693475, correct?

A. The meaning is of this is to be evidence how you could start with the material obtainable following the procedure giving this example. This is the meaning.

Q. So you are telling the Patent Office that the work that you did for example 25 is the starting material for this example in the '364 patent, correct?

A. This is one way to obtain the starting material to make this experiment that is mentioned here.

Q. In the patent, this is the '364 patent, it doesn't say here what polymorphic form was the starting material of example 25, correct?

A. This is correct.

Q. Did you personally check to see what polymorphic form this was?

A. No, this was done not by me.

Q. Dr. Gruss did the work?

A. Dr. Gruss and others.

MR. ALY: Thank you, your Honor. I have no further questions.

THE COURT: Thank you. All right. We've concluded with the cross by all defendants. So would you like to redirect?

MR. BEST: I would, your Honor, but fairly brief, I think.

THE COURT: All right. Go ahead.

REDIRECT EXAMINATION BY MR. BEST:

Q. Hello again, Dr. Buschmann.

A. Hello again.

Q. Could I have, Rob, on the screen the demonstrative from plaintiffs binder Page 32 on the split screen with Page 18, also a demonstrative?

So, starting with, we can use batch one for the moment. Now, do you recall Mr. Aly asked you some questions about the

final step of the synthesis transforming BU351 into BU322?

A. Correct.

Q. And he also asked you that in the context of the rest of the synthesis of batch one.

Do you recall that?

A. Yes.

Q. So, if there were impurities that resulted from the prior step of the synthesis of batch one, could they have been carried through to the end, end product of BU322?

A. So, any of the intermediates which were done were isolated. And following, if I could start with the first step, the first step is to make the grignard (sic) reaction the grignard reaction starting with manage base of pentanone resulting in the addition of product which is called the grignard product.

But here also the two stereoisomers were formed. Predominantly the air is low as the 301, then the purification was done using this step BU41 to form the hydrochloride. So it was then the confirmation that only the threo form of the racemic product was isolated.

Following then the next procedure that means impurities of the 301 were eliminated with the best technical spectroscopic method to check the purity. But with NMR, none of these other diastereomers were detectable. That means it was considered as a purity of higher than 99 percent which is

the detection rate of hydrogen in this case using the machines.

Secondly, then this product which was already considered as a purified product, was separated in the enantiomers given chiral H P and C and so it is in a way an additional purification process. And then the material, after the racemic resolution was crystallized again, which any crystallization is a purification process at the end.

So also then the additional purified enantiomer as a solid was used for the next step. And this was then transformed to the chlorine derivative. And as the chlorine derivative was also purified before putting it through the next step, having it in the flask and eliminating all things around the reagent and so on.

And then the methoxyl derivative was also used as hydrochloride. And hydrochloride means also a crystallization process has taken place which means also purification. So that means before the last step was done, I would consider a pure compound was transformed into last steps.

Q. And when you say a pure compound, do you mean?

A. Pure or purify. Any drug on the market is not pure. You have always a range that means pure enough. That it's considered as the molecule you are believing they are. That means somewhere between 95 and 99 percent is normally considered as pure.

Q. And if I could have batch 0 up. Slide 18, to the

extent there were any impurities that were carried through to the final product, would you have expected them to be essentially the same following the batch 0 synthesis as batch one?

A. Yes.

Q. Now, could I have DTX 972 up? Actually could I have on split screen DTX 972 on the left and PTX 312 on the right at Page 9605, GRTNUC 9605.

And if you could blow up example 25 on the right hand document.

Unfortunately the print quality is fairly poor. But, I believe you can tell that there's an optical rotation at the bottom. Do you see that?

A. Yes.

Q. Do you recall Mr. Aly asking you questions about some of the data including the optical rotation?

A. Yes.

Q. And you see that number. What is the number that's been reported in the patent for the optical rotation?

A. 27.5 degrees.

Q. Now, if I could ask our videographer on the lower right-hand side blow this up. Do you see the numbers indicated here?

A. Yeah.

Q. Are those the same numbers that appear in the patent

for example 25?

A. This is correct.

Q. And on the left, what is the chemical reaction that's being shown?

A. This is last step following to the solid of Tapentadol hydrochloride.

Q. Now, could you clear the blow ups please.

And could you on the right hand put up PTX 977? Actually it might be DTX 977. Could you blow up again the optical rotation numbers?

And do you recall Mr. Aly asking you questions about how this number differs from this number?

A. Yes.

Q. Did the difference between these two numbers give you any uncertainty as to whether you had Tapentadol on each occasion?

A. Not at all. For a chemist it's exactly telling you you have the same.

Q. Why is that?

A. Because of the variants measures the optical rotation, the temperatures, really the amount you are using for the measurement and the quality and a lot of parameters influencing it. So for that compound report you will find several optical rotation values which are then in the range plus minus minus 26 and minus 27 point something for a chemist was exactly the

same. It was a confirmation it is the same because the direction of the optical rotation and the method of order was the same and it was important.

Q. Can you clear PTX 306 on the left. Can you put up on the same document on the right now on the left? Could I have page ending in 9311 and could we have 9333 on the right?

You see here some structures associated with example two, correct?

A. Yes.

Q. And on the right I believe you recall Mr. Schuler asking you about example 25 at some length?

A. That's correct.

Q. Now, I believe you testified that there were methods of confirming that in response to Mr. Schuler's questions that there were methods of confirming that you had obtained this product as a result of the chemical sequence of reactions that you had done. Is that right?

A. Yes.

Q. Is it the case that one of those methods of confirming that you had obtained this product was knowing this starting material minus one in example two, as well as knowing the sequence of chemical reactions that you used?

A. Exactly. Both sets together were used.

Q. Now , could I have DTX 736 up?

Now, you may recall, although it's been a few hours,

Mr. Capuano asking you about this document, DTX 736.

Do you recall that?

A. Yes.

Q. In particular, do you recall him asking you about this information dealing on certain activities of various enantiomers of Tramadol and O desmethyltramadol? Do you recall?

A. This is correct.

Q. I think in the context of that conversation in answering his questions you used the term, you used the term in vitro and in vivo results.

Could you explain what you meant by those?

A. What it means different in vitro results could refer to different complete different in vivo observations specifically based on opioid ligands.

Q. If you need a moment, please feel free to do so. But, are the data that are reported in this paper from in vivo experiments or from in vitro experiments?

A. As far as I have seen this paper they are based on in vitro data.

Q. Could I also have up now the Flick article DTX 834? And I imagine you recall Mr. Capuano asking you about the 1978 Flick paper, correct?

A. Yes.

Q. Now, do you know roughly how many compounds were

synthesized and recorded in the Flick article?

A. It's around 25, 27, something like this was a limited set of compounds which were available summarizing this article at this time, at least as I was told.

Q. And at this time do you mean around 1978 when it was reported?

A. Yes.

Q. Now, in between this period of time, in between this period of time and your beginning at Grunenthal in 1992, do you recall about how many compounds had been synthesized in the Tramadol successor project?

A. In the '91 paper around 550 compounds were synthesized. And I joined in May '92. At this time it were around 700 compounds which were represented to me look that we have done already.

Q. If you need to look through the paper, please feel free to do so.

But, are any linear backbone compounds reported in this paper or are all the compounds possessing this cyclo --

A. I have not seen any in the compounds. And maybe I have to add additional comment because this paper was published in '87, but the data, the test model and the compounds which were tested are much older. So that means this was not available in '87. It was the compilation of work which was done years before.

Q. Are there any linear compounds reported in those papers or are they all cyclical backbone?

A. I haven't seen any in here.

Q. Now, you may have mentioned in responding to Mr. Capuano's questions particularly about L 201 that there is a mixture of diastereomers. Do you recall that testimony?

A. Yes.

Q. Now, would a mixture of diastereomers have had any effect on the animal model experiments that were performed in the paper?

A. Yes because if you have a mixture of compounds, a composition of the mixture will have an effect on the outcome of this experiment.

Q. And does Tramadol possess all four of those diastereomers in the ingestible form?

A. Using the L and E code, it was considered. It was a diastereomeric mixture which was measured.

Q. So, sorry, perhaps my question wasn't clear.

When you say that there's a diastereomeric mixture, for example, L 201 in this paper, how many compounds do you mean are a part of that mixture?

A. So, diastereomeric mixture means at least four different stereoisomer were present. And this was the result of stereochemistry of the grignard reaction (sic) which was resulting in the 822 ratio of the so called trans enantiomeric

pairs and to the assist the enantiomeric papers.

So that means at least it was 4411 mixture of compounds consistent with knowledge, investigating the industrial knowledge of the Tramadol that was considered as diastereomeric yield.

Q. And the drug Tramadol does it only contain two of those stereoisomers?

A. This is correct.

MR. BEST: I have no further questions.

THE COURT: Thank you. All right. Thank you. Mr. Capuano.

MR. CAPUANO: One ten second question.

THE COURT: That's fine. Go ahead.

RECROSS EXAMINATION BY MR. CAPUANO:

Q. Dr. Buschmann, I just want to clarify, you mentioned in the Flick paper that it was published in 1987. I think you meant 1978. Is that right?

A. I think that's right.

MR. CAPUANO: No further questions.

THE COURT: Nothing?

MR. BEST: I'm done.

THE COURT: We are concluded with this witness. Thank you very much. You are free to go. Thank you, sir.

THE WITNESS: I enjoyed.

THE COURT: We did as well. Thank you. You may

step down.

MR. GLANDORF: We have our next witness ready.

THE COURT: I think given what's going on, we need to proceed.

MR. GLANDORF: David Glandorf from Gibson Dunn representing Depomed.

THE COURT: Are you ready? Do you need a few minutes?

MR. GLANDORF: We need a couple of minutes to grab the witness. A quick break would be good.

MR. SITZMAN: Before we break, and by the way --

THE COURT: Hello.

MR. SITZMAN: I actually think we need to take a break and talk with the defendants because I don't think any of us thought that we would be here at 5 o'clock and not having put Dr. Gruss on. I am assuming defendants still want to put two of their witnesses on tomorrow. And I think there's going to have to be some discussion.

THE COURT: Why don't you do that. Why don't you talk to one another in the break, see how you want to proceed. Obviously I'm here later tonight so we can do whatever we need to do. But, you know there might be reshuffling.

MR. SITZMAN: Yes. Thank you.

THE COURT: Thank you.

(Whereupon a short recess was taken.)

THE COURT: So, let's do a very quick update as to where we're at so everyone understands what the schedule is going to be. Its sounds like we're going to have a very busy day tomorrow. And we are going to have a number of witnesses who have very difficult schedules involving complex schedules. And we are going to accommodate.

Everyone's going to come in at 8:30 tomorrow morning so we can start early again. I'm happy to stay late tonight. But I understand the parties spoke and discussed how they want to proceed with the next witness. And I think the preference is that you do direct tonight and cross in the morning.

I have gotten an estimate about an hour for direct and maybe an hour and a half for cross. That's a rough estimate. We will see how that goes. But, it's also my understanding that we have two additional witnesses. Is it two additional?

MR.FITZPATRICK: Three.

MR. SITZMAN: Three.

THE COURT: Three more. In any event, I am going to be here. I'm happy to accommodate you. How you spend your time obviously is a decision for you folks. And knowing who the witnesses are and the schedule that you will have to act accordingly. I leave that up to you how you want to divide the time. I'm fine to stay if you'd like to stay longer.

But, I understand it is in fact the preference of the parties that you're just going to do the direct. You're going to start with the cross in the morning, which is okay by me. Let me hear from you folks.

MR.FITZPATRICK: This is the preference.

THE COURT: This is the preference. All right. And I know it's very warm in here. We are trying. We're going to open the doors here into the hallway. It's a secure hallway. There's no one out there. Just to get a cross ventilation. That might help us out a little bit.

So let's turn to the plaintiffs. Call your next witness, please.

MR. GLANDORF: Plaintiffs Dr. Michael Gruss to the stand. I believe we have some document issue objections.

THE COURT: You have objections. Go ahead.

MR. ALY: Two sets of objections, your Honor. One is PTX 1547 is a newly produced colored and more precise version of XRD polymorph produced on February 22, 2016 so 2 or 3 weeks ago. And basically we will not object to it as long as now we can use it and process it in the trial. It's only fair.

THE COURT: I am sure there's no objection to that.

MR. GLANDORF: No objection.

THE COURT: That sounds fine. What's the next one?

MR. ALY: The second one, there are six files that were produced during discovery with tables about an inch and a half thick of two plot, excel kinds of plot numbers with data, raw data files. But basically now they are being used at trial.

We ask for the raw data file that goes with the text that are printed out. And plaintiffs said we should have asked during discovery. I would just rather have those raw data files to plot themselves ourself.

MR. GLANDORF: That's correct. They asked for these at 10 o'clock last night. We don't have the raw data files. We provided the files to them in discovery. The files we provided do have the, you know, they are just text files. They are just rows of numbers is what they are. And when we provided it to them during discovery, those files were text searchable meaning the text was extractable.

So they easily load those into excel or any database program. They have the files available.

THE COURT: I was going to say if you have them provide them. You can give them after hours. Do you have them back at the office? Does anyone?

MR. GLANDORF: My understanding is that we don't have them.

THE COURT: You don't have them?

MR. GLANDORF: But again all they are are rows of

numbers. And so you know the files we were providing them the text. They have them. Anything they need to plot them --

THE COURT: Explain to me again what is the difference between what you are actually providing and the native documents themselves? What is the difference?

MR. GLANDORF: I could show you the documents if you'd like.

THE COURT: Bring it up.

MR. GLANDORF: You have the binder there in front of you if you turn to page for example PTX 0602.

THE COURT: PTX what is that?

MR. GLANDORF: 602.

THE COURT: All right. How would the underlying data look any different.

MR. GLANDORF: It wouldn't, your Honor. I think this is just data you can plot in whichever kind of software you want. It would just be data that you can load directly. And that's my understanding is that's what they have with the extracted text.

THE COURT: All right. It sounds like this is the best they can do in terms of this. So you know you have the exhibit here. You can use it however you'd like to use it. To the extent you go back to your office and you do determine you have something further with respect to this, just provide it tonight.

MR. GLANDORF: We will.

THE COURT: Okay.

MR. ALY: One thing I heard newly perhaps was they suggested was an extracted text file could be, in order words, they would scan the text in this paper and then we get an electronic version. That maybe if plaintiffs provide that tonight, if they can't get the negatives. At least there won't be dispute --

THE COURT: You're fine with that? Can you do that?

MR. GLANDORF: That is what we gave them originally in discovery.

MR. ALY: We have what we are referring is OCR version from the production.

THE COURT: You are looking for an actual scanned one of these that you can search through.

MR. ALY: Precisely the scanned version which would provide the text column so that there won't be dispute about the OCR being incorrect or correct. It would just be here, the text numbers of two columns and do what we want with it.

THE COURT: So you can agree.

MR. GLANDORF: I'm a little confused as to the difference between that and what we have already provided.

MR. ALY: I think we got the papers. I am asking

for the electronic file.

MR. GLANDORF: You didn't get the electronic file during discovery?

MR. ALY: That's what this dispute is about. We want to make sure you send it. Maybe we can continue talking about it, do a meet and confer so we can continue having a discussion.

MR. GLANDORF: When we provided the Gruss discovery it had the extracted data file with it.

THE COURT: Maybe it just got misplaced.

MR. ALY: I think we have a misunderstanding of what was provided but we will figure it out.

THE COURT: You will try and work it out after this point.

MR. ALY: Absolutely.

THE COURT: Anything else? No? Okay. Let's start.

M I C H A E L G R U S S, sworn.

DIRECT EXAMINATION BY MR. GLANDORF:

Q. Good afternoon. Could you please state your name for the record?

A. Michael Gruss.

Q. If we could, let's put up exhibit, plaintiff's Exhibits 1458.

A. 1458.

Q. Go to the back.
A. I have it.
Q. Dr. Gruss, do you recognize this exhibit?
A. Yes.
Q. What is this exhibit?
A. It's a United states patent number U.S. 7,994,364. Q
Q. What is your relationship to the patent?
A. I am named inventor on this patent.
Q. Who are the other inventors?
A. Other inventors are Andreas Fischer, Helmut Buschmann and Dagmar Lischke.
Q. In your own words, could you tell us the intent of the patent.
A. It is crystalline form A, Tapentadol hydrochloride, which is subatomically stable at room temperature and more stable than the other known form B.
Q. More stable than form B. Is that what you are saying?
A. Yes.
Q. Dr. Gruss, can you tell us a little bit about your educational background?
A. Yes. I studied chemistry in 1989. I started my studies at University of Giessen. I did my diploma series in 1995 in organic phosphorus compounds and continued my studies and finished with my Ph.D. in 1998. Yeah.
Q. You are from Germany?

A. I am from Aachen. So English is not my first language. So I might ask you maybe for slow down or repeating questions.

Q. Okay. In your doctoral studies, did you specialize in a particular area?

A. Yes, I focused on inorganic phosphorus compounds, determination of the single crystal structure, the characterization for example of bio x-ray powder diffraction and yeah.

Q. Where did you begin your work after you obtained your Ph.D?

A. I joined a small company in Germany Yasservitzen Carr KG (ph) in 1998 and finished the work there in April 2000 and joined Grunenthal GmbH in May 2000.

Q. Are you still at Grunenthal currently?

A. No, I left Grunenthal on 31 July 2015.

Q. Where are you currently employed?

A. I founded my own business Solid State Concepts in September 20th as a consultant.

Q. What was your position at Grunenthal at the time you left the company?

A. I was head of laboratory in the process development department.

Q. Let's go back to the beginning now. What were you hired to do at Grunenthal?

A. I was hired for two fold positions, first chemical

data manager and secondly I was, yeah, hired to establish solid state facilities at Grunenthal.

Q. What do you mean by solid state facilities?

A. Solid state facilities there was intention to investigate polymorphism solid screening and crystallization optimization studies. And so I was asked to build that facility up to do a more systematic investigation of that matter.

Q. I'm sorry, did you say more systematic investigation?

A. Yes, yes.

Q. You mentioned polymorphism. What is polymorphism?

A. Polymorphism is the ability of a compound to crystallize in more than just one crystal structure or just one more form.

Q. Could you tell us at a high level what is involved in a polymorphism investigation?

A. So polymorphism investigation is to apply various parameters on the crystallization like temperature ranges, like various solvents to extend as broad as possible range of investigations in order to understand and characterize the compounds or the compound under consideration.

Q. What analytical techniques do you use in a polymorph investigation?

A. So, for the formation part so you do some crystal separation using a crystal tool or some mechanical or some

studies. And what you also do from the analytical point of view you do characterization by x-ray diffraction, especially x-ray powder diffraction, x-ray single crystal diffraction and to apply some analytical technique like DCSSTGA or variable temperatures, spray powder diffraction or hot stage microscopy. And in addition, you apply spectroscopic methods.

Q. Let's talk about a couple of those if we could. What is an x-ray powder diffraction?

A. X-ray powder diffraction is a technique where you can get a fingerprint of the crystal structure so you x-ray on the sample, rays get diffracted and then you get, yeah, specific pattern diffraction pattern of that compound.

Q. Now, would a person use XRPD alone to investigate polymorphism?

A. Usually not. So what is important is that there are various techniques in the game and every technique has a specific strength. Nevertheless xray powder diffraction is the method of choice, so called gold standard. But, in order to fully understand the system, you also have to sometimes apply additional methods. Like, for example, DSC.

Q. Can XRPD distinguish between different polymorphs?

A. It depends. So it depends on the system of polymorphs you are considering.

Q. And what is single crystal diffraction?

A. Single crystal diffraction is also a diffraction

technique. With this technique you get a better understanding of the arrangement of the atoms in the crystal.

So, yeah, it's an investigation done on the single crystal what the name states already, yeah, differentiation to the powder diffraction where you investigate multiple crystals.

Q. You mentioned a technique known as DSC. What is DSC?

A. DSC stands for differential scanning calorimetry. That is a method where you apply heat to the sample and you have to look at what happens with the sample.

So in comparison with reference center you, for example, if a sample melts or if it fades, transformation, which means polymorphs, changes from one form to another.

Q. Let's go back to when you started at Grunenthal. Did your position exist before you arrived at Grunenthal?

A. Not to my knowledge.

Q. Was anyone conducting solid state investigations before you arrived at Grunenthal?

A. There had been several investigations performed. For example some sole analytical studies. There had also been some samples out for trace characteristic situation but not as a systematic manner as I would have understood it.

Q. You were the first one to do systematic investigations. Is that right?

A. At Grunenthal I would say so.

Q. When you joined in 2000 was there a solid state

laboratory there?

A. No, not with respect to the formation studies. There has been a laboratory but for example a DSC or TJ was already available but no systematic investigation of the formation of crystallization studies. That is something I established as time went by.

Q. Do you know who was conducting the non systematic solid state investigations before you arrived?

A. Yeah. For example, Dr. Lischke did some studies, some early studies with DSC also with TGA who sent the, I seen various people who sent out samples for x-ray diffraction. But I can't remember who they was in particular.

Q. What was Dagmar Lischke's position at Grunenthal?

A. To my knowledge she was a technician in the department of analytical chemistry.

Q. Who was your supervisor when you began at Grunenthal?

A. When I joined at Grunenthal it was Dr. Helmut Buschmann.

Q. When you started there how many compounds did you begin investigating in a systematic way for polymorphism?

A. I would say a handful.

Q. And does that include all of the compounds under development at Grunenthal at the time?

A. No, no, we started, as far as I remember, with 2 or 3 compounds with the systematic studies because it requires a lot

of effort and resources. So you cannot do everything at once.

Q. Was one of those 2 or 3 compounds initially investigated, Tapentadol hydrochloride?

A. Yes.

Q. And were you involved specifically with the Tapentadol project?

A. Yes.

Q. When did you become involved with Tapentadol?

A. I think that was right at the beginning from the 2001 time frame.

Q. Was there a core group of people that were working on the Tapentadol project at that time?

A. Yeah, I would say so.

Q. Who was that?

A. I would say that's Helmut Buschmann, Dr. Fischer and Dagmar Lischke.

Q. And we talked a little bit about Miss Lischke. When did Dr. Fischer join Grunenthal?

A. As far as I know he joined in 2001. He was, first he was with a contract research organization. So, he was an external expert for Grunenthal doing x-ray investigations. But then he joined in 2001 as far as I know.

Q. Do you recall where he was working when he was working initially with the company?

A. Yes, the name of the company is F plus E analytics.

Q. What was his position at Grunenthal when he joined?
A. He was joined as head of laboratory of the center state laboratory in the analytical department.
Q. Going back, you mentioned some non systematic solid state analytical work had been done.
Had any of that work been done on Tapentadol?
A. Yes, I think Tapentadol, as far as I know, was amongst the composites that has been investigated.
Q. And did you gather together that work when you joined your job?
A. Yeah, when I joined at Grunenthal one of my duties was to get together the material that has already been produced on the compounds, which means I was asked to collect, yeah, the folders, for example, for x-ray diffraction. And that was sort of my sub word. And I also collected information about Tapentadol hydrochloride and for example some of the analytical studies.
Q. Was that work Miss Lischke had done?
A. As far as I know, yes. So at that point in time I think as far as I know she started to play with the machine and to understand how that works.
Q. Which machine?
A. On the DSC machine and the DGI machine.
Q. Based on her early work, do you know if she had an understanding of whether Tapentadol hydrochloride was

polymorphic?

A. At least she had the suspicion that 5 or 6 modifications of Tapentadol hydrochloride existed.

Q. And did you then collect new data on Tapentadol?

A. Yes, from starting, yeah, 2000, 2001. As I mentioned we started collecting samples and we produced new samples, the new formations of solids. And there was a continuous work yeah until more or less I left company.

Q. Where did the samples come from that you collected?

A. In 2000, 2001 time frame so when we, after the samples have been already created at Grunenthal, I think they came from various departments.

Q. And did you reach any conclusions regarding Tapentadol?

A. Yeah. So in contrast to Dagmar Lischke who had just limited possibilities with respect to analytical data, she just had some of the analytical data. When I reviewed the other x-ray data and the more information we got, I drew the conclusion that there are two polymorphs.

Q. Do you recall the time frame in which you understood that there were two polymorphs of Tapentadol?

A. That must also be in the 2000, 2001 time frame, yes.

Q. And how did you -- strike that.

Did you help prepare a slide that shows some of the dates that we mentioned?

A. Yes.

Q. Can you bring up the first PowerPoint slide? Is this that slide?

A. Yes.

Q. You mentioned that you collected samples of Tapentadol. Which polymorphic form was present among those samples?

A. So, there were various recipients various powder particles and I would, among those samples would have been the forms that we know as form B and form A and also mixtures of A and B.

Q. There was some were A, some were B and some were mixtures of A and B. Is that right?

A. Correct.

Q. So was your study complete after you determined that there were two polymorphs of Tapentadol hydrochloride?

A. No, no, the grignard indicates the Grunenthal investigations. And I said that before it continued through over the whole time period. And so there was, as time went by, the more and more experiments we did, the more information we gathered.

And from my understanding the polymorphism screen or polymorphism investigation on the compound was never finished because you never know, maybe after a hundred years you might experience a new form.

Q. Let's talk for a moment about the samples you collected when you started. Do you know if Grunenthal kept all of these

samples through the end of your employment there?

A. To my knowledge, so you must see that samples are used up during analytics. For example, that can be generally laboratory started up like you do at home. And 2010 time frame Grunenthal became a control substance and yeah was that respected. We had to prepare all the laboratory so we disposed of some samples just in order to follow according to German law.

Q. So, how did you proceed from there with your investigation?

A. So, from you mean from 2000 on?

Q. Yes. From the point where you had determined that there were two polymorphs.

A. Okay. So we continued. First our mission was to introduce the concept of solid state investigation into the company and to raise awareness that it is important to investigate this solid state.

So, I talked with people and asked them yeah, forward the samples to the analytical department so that they can investigate. Or send them to me so I can send it for x-ray investigations. What I also did, we initiated systematic polymorphism investigations with an external company.

Q. What external company was that?

A. That was SSCI located here in the U.S.

Q. Did you decide to hire SSCI?

A. That was a joint team decision. And yeah, we visited SSCI, I think Michael Finkus (ph) and Helmut Buschmann and I don't know if there have been others also being with us, so we inspected them to get an impression of SSCI. So because I haven't been to many companies doing such investigations and then we decided to do that with SSCI. So it was Grunenthal finally hired SSCI, not me myself.

Q. Did you recommend that they hire SSCI?

A. Yes. We had a very good impression from SSCI so there was a good reason to let them.

Q. Why did you make that recommendation?

A. Why? So, as I mentioned before, it was a joint team decision. And yeah, why did I do so? There were just a few companies on the market, as I mentioned before. And SSCI had a good reputation as well and yeah, we saw that might be a good way to proceed with good investigations and to cover as much as possible to understand the system even more.

Q. What is the purpose of the SSCI investigation?

A. The purpose of the investigation was to conduct the systematic polymorphism investigation, what I mentioned before, to apply different techniques for the crystallization and all that stuff.

Q. But, you already knew at this point that there was a form A and form B. Is that right?

A. Yes, yes. I remember very well that at that point in

time we had, for example, determined the lattice parameters of form B. And we had a single crystal structure investigation done on form A.

Q. Do you recall an external company named Crystallics?

A. Yes.

Q. Did you hire Crystallics?

A. That was a bit later. So not me but Grunenthal hired Crystallics in order to conduct more investigations on the crystallization of Tapentadol hydrochloride.

Q. Did Grunenthal eventually get its own XRPD machine?

A. Yes.

Q. Do you recall when that was?

A. I think that was in 2003 and another I think in 2006 as far as I know.

Q. And did you help to add these events onto the timeline as well?

A. Yes.

Q. Is this timeline accurate, to your knowledge?

A. It appears to be so that, yes.

Q. Do you recall a sample named batch 0?

A. Yes, very well.

Q. What was batch 0?

A. So, batch 0 was a sample that has already been produced in 1994 as far as I know in the lab of Helmut Buschmann. And I think that was among those samples that we sent out in 2000 ,

2001 time frame. I say 2001. And when we received the results or I received the results, I remember that I discussed that with Helmut.

And because that was surprising that the form B and after 7, 8 years of storage, we still had form B on our hands. So, that was the point where we realized that form A is a new one actually at least I indicated that.

Q. Let's go back and break that down a little bit. You said you sent batch 0 out. What did you send it out for?

A. For x-ray powder diffraction analytics.

Q. Let's bring up now, let's bring up 646 and the translation of 646T together if we can.

Do you have those? They are kind of small. Do you have those in your notebook?

THE COURT: Can we just go back to the timeline for one moment where you have the section that says May 2000 where you joined Grunenthal. And then there's sort of a star graphic determination that two polymorphs are present.

Could you just again recite for me the information you relied on to create that entry into this chart?

THE WITNESS: So, there has been investigations ongoing like to some analytics but Dagmar Lischke had the suspicion about 5, 6 forms just based on the events she observed during some analytical studies. And when I joined there has been --

THE COURT: When was that? That was her looking at it in? She started in 1998?

THE WITNESS: As far as I know, yes.

THE COURT: So when would it be that the determination was made, this is May 2000, that there may be two polymorphs present?

THE WITNESS: Yeah, the point is I started to put also together the x-ray poly diffraction data. So we had investigated. I realized there's not just two different patterns, form B, and form A and a mixture of the form A and B. And that can be examination was analytics done in the DSC.

THE COURT: Now is that what you did or something she did in terms of making a determination?

THE WITNESS: I would say it was a team effort. Because I had discussions with all the staff. For example, I remember well that I discussed with Dagmar when I understood an event in the DSC. I understood that that was a phase transition.

And I remember very well the moment because there was a point when she realized that yeah, I might not just be a doctor but also can discuss the scientific manner with her.

So, I was the one who brought the additional x-ray diffraction data and draw the conclusion that there are not 5 or 6 but just two polymorphs in the game. And that is polymorphs are, that's what she saw in the DSC is a phase

transition, a solid phase transition between A and B.

THE COURT: The DSC again, what is that?

THE WITNESS: Differential Scanning Calorimetry which is an analytical method. If you like I can shortly explain.

THE COURT: Yes, definitely.

THE WITNESS: I'm not an analytical expert.

THE COURT: It's the application of heat, no?

THE WITNESS: Right. You have two samples you measure there's a difference in heat that for example takes up, if the example crystallizes, is released. So you compare that with what your sample does.

For example Tapentadol was a reference standard then you see for example there is a phase transformation or for example you can see that a solvent is lost, not in the case of Tapentadol but in other or you can see for example that the sample melts.

THE COURT: Thank you.

THE WITNESS: So there are various events.

THE COURT: Thank you.

THE WITNESS: Pleasure.

Q. So I think we had the document translation side by side here.

Dr. Do you have those documents in your binder there as well?

A. I am on 646 should I go to the translation or.

Q. It's up to you. It's your choice but for the Court I think we will be showing the translation. If we can just --

A . Okay.

Q. Do you Dr. Gruss do you recognize exhibit plaintiff's Exhibit 646?

A. Yes.

Q. And what is this exhibit? It's a document?

A. An document, a letter that I sent along with the examples to Professor Gernot Heger, professor of crystallography Professor at Aachen university for the Kaiser who did the investigation. At that point in time was Gernot Heger institute.

This is a letter where I sent the sample BN 200-0 to their attention. And furthermore what I always did is I asked them to measure the powder diffractogram, the stray powder diffractogram of the samples. And this translation is a bit or I would say if I would have translated it differently.

I said please do not apply any mechanical or thermal stress to the samples prior to the measurements. This says just as little as possible. But I would say no, so that would be my translation.

Q. I see. Let's turn now to exhibit plaintiff's Exhibit 559 if we could. And let's put the German version next to it as well. That's fine. Actually let's do that.

Do you have Exhibit 559 doctor?

A. Yes.

Q. Do you recognize this document?

A. Yes. That's a relaunch from Dr. Kaiser who sent with me back with the results.

Q. And does this include batch 0 as well?

A. Yes, it says there on when you say Number 87452 yes it includes B into one of batch 0.

Q. Can you read for the Court the two sentences that are written about batch 0?

A. Okay. The poly diffractogram of samples listed below were recorded and if need be, compared with calculated powder diffractograms from E K data. E K stands for single crystal. So that's German wanik crystalline (sic), I suppose.

Q. And this next sentence here starting at capillary?

A. Capillary Geometry had to be used because of very small sample sizes. The sample was very difficult to read and required very long measurements times.

Q. And again this is batch 0 of Tapentadol hydrochloride. Is that right?

A. Yes.

Q. How do you know that?

A. Because on the original, so when I sent it out. The sample name is BN 200 hatch 0 and BU 322 minus one minus one-HCL.

Q. What is the date that you received this data back ?
A. The date on the letter is fourth of February, 2002.
Q. Do you recall when batch 0 was synthesized?
A. Yeah. As I mentioned before as far as I know it was synthesized in 1994.
Q. So this is over seven years later that you had the results back. Is that right?
A. That is my understanding.
Q. Do you recall reviewing the XRPD pattern of batch 0?
A. Yes.
Q. Do you recall your conclusion?
A. Yes.
Q. What was your conclusion?
A. My conclusion was that BN 200 is form B.
Q. I think you mentioned this already but just if we, if I could ask again what was the significance of batch 0 to you?
A. So the significance of batch 0 was first of all that was already produced 7 or 8 years before it had been sent out for x-ray. And it indicated that, no, and yeah, after that long period of time, it was still form B.
That was very interesting because at that point in time we understood or that form A is new.
Q. Let's go ahead and bring up plaintiff's Exhibit 1547.
A. Which one. Sorry.
Q. 1547. Dr. Gruss do you recognize Exhibit 1547?

A. Yes.
Q. What is this exhibit?
A. It's a comparison of two powder diffractograms of BN 200.
Q. So there's two patterns on here. Is that correct.
A. I see two.
Q. Let's start with the blue. What is the blue pattern?
A. The blue pattern is the x-ray powder diffractogram of NH 1 with batch 0.
Q. And what is the red pattern?
A. The red one is reference pattern we used for form B of a batch called CEPM 1 A. So that's a sample we had drawn from that batch.
Q. So CEPM1A here is the reference standard for form B?
A. It's reference pattern that we used.
Q. Reference pattern for form B?
A. Yes.
Q. What can you conclude if anything from this exhibit?
A. That there's no form A in BN 200 batch 0. So batch 0 is form B.
Q. Do you see any form A in the blue pattern?
A. I don't see any form A in BN 200 batch 0.
Q. Is this consistent with your memory of the results when you reviewed it at the time?
A. Yes.

Q. We're going to bring up now two exhibits side by side which is 574 and 602.

THE COURT: Just go ahead to 1547 for a moment. Is it your conclusion that it's form B because it matches the reference form CEPM. Or did you also conclude that it's form B based upon expected characteristics as to what this was supposed to look like?

In terms of what you thought that this pattern was going to look like, did you have any sort of preconceived notions in terms of what you thought the pattern might look like through this analysis? Or is it simply that you had the reference form, this CEPM so you already knew that was form B? You looked at it and matched it up?

THE WITNESS: I see I have to explain how that worked. It has been done. So, in general you start with you have to have a sample you x-ray, then you get a pattern. That is everything you have at the beginning.

If you have several samples you get different patterns. And one method of choice during polymorph studies for example is to compare those patterns and see and group them together, similar patterns and similar groups.

So, for example in the case of Tapentadol we had form B, form A and mixture that would state 3 groups. And the more patterns coming, you put them into the groups. So that's first of all. And then you see there are three groups and then

you, but you don't know at the beginning is maybe the mixture of A and B also maybe probably a new form. But then you can compare and see okay, all the peaks in the mixtures are coming up also in A and plus B you see. So that's an overage of the peaks when I put my fingers together like that.

But then the investigation go further. For example we had, if you have, you can with technical method you can determine the lattice parameters. That is something I did with form B on that pattern. And based on the lattice parameters you can calculate theoretically where the peak positions are on the two patterns.

And we had the x-ray single crystal structures form. And with a single crystal structure you can do even more. You can calculate the position of the peaks and the intensity of the peaks with the lattice parameters. You can just calculate the position.

What I then did is I put the parameters of A just in case to understand it a bit better, I was just playing. And also the lattice parameters of B. And then the stimulation of B as well, that is not really accurate but it's similar. And then you can also get an impression about intensities of the peaks.

So, having that knowledge in mind, I compare the pattern. And I can't remember exactly but I might have also compared this pattern with A and saw that there was no A in B.

THE COURT: Okay. And just looking at the red lines just so I understand how your analysis works, the red line at the bottom, the fact that it's a little bit lower than where the blue is, does that matter at all?

THE WITNESS: You mean so on the left part it's a bit higher than the blue one on the right part.

THE COURT: I will show you right here. Come over. So right down there, does this matter that this is not falling exactly on that line? I'm pointing to the red line under the -- on the right side. Does that matter?

THE WITNESS: No. So that depends on the sample and how it is. So you see like here there is an above and below. What is really important in the x-ray is the position of the peaks. And the intensity can be a bit varying depending on how the crystal shaped, for example.

THE COURT: Does this matter, for example here that this red peak is in excess of what the blue is?

THE WITNESS: That is higher.

THE COURT: Yes:

THE WITNESS: No not at all.

THE COURT: It matters where the position is.

THE WITNESS: Right.

THE COURT: And that's --

THE WITNESS: These match really well from my understanding.

THE COURT: Thank you. Thanks.

THE WITNESS: Do you need some more explanation?

THE COURT: No unless you have anything else you might want to add.

THE WITNESS: For example, so if you have a pile of papers, if you have crystal which then you, it could be simulated pattern is not as accurate as the measure because the distances here are all the same. Generally you have a sample that goes like that. So you have better diffraction. I have mixed it up.

THE COURT: I got it. Thank you.

THE WITNESS: So what I mentioned is the intensity.

THE COURT: Again the conclusion is this is a clear form B.

THE WITNESS: No form A.

THE COURT: No form A. Thank you.

MR. GLANDORF: No problem.

Q. Are you ready doctor?

A. Yeah.

Q. We were looking previously at Exhibits 574 and 602.

A. Sorry.

Q. And realize these are large exhibits. Do you recognize these exhibits Dr. Gruss?

A. Yes.

Q. What are these exhibits.

A. 574 is a copy of a UDF file from BN 200 batch 0 first reporting. 574 and Exhibit 602 is an X Y list derived from that UDF file.

Q. And what is a UDF file?

A. A UDF file is a data file that was put out from the x-ray diffractometer at universities of Aachen. And in order to get a pattern I had to derive the X Y pattern which I could load in the Excel and get the representation.

Q. So the X Y data on the right is derived from the data on the left. Is that correct?

A. Yes.

Q. The X R data is derived from the UDF data?

A. Yes, that is.

Q. My understanding is that is XRPD data itself. Is that correct?

A. That is the intensity measured by the x-ray diffractometer like the height of every single point in the pattern, the pattern you showed me.

THE COURT: They is showing the peaks?

THE WITNESS: Not peaks, it's showing the complete so if you --

THE COURT: Do you want to put up the last one.

THE WITNESS: Your pattern, so every single point when you have the peaks, the numbers are even higher in this

list.

THE COURT: Hold on 1 second.

THE WITNESS: I try to --

THE COURT: All right. So, if we are looking at this last exhibit.

THE WITNESS: Yeah. For example so if you, in the X R, let's say X Y, that's even simpler this just from 5 to 14 that I mentioned. But, for example, if you step through that another file list it's position five must be an intensity. And if you step through, you get at one point the high intensity.

MR. ALY: Your Honor, I'm sorry to interrupt, is it all right if I go watch to see what's there so if I want to cross?

THE COURT: Come. I have taken plaintiff's trial Exhibit 1547 and I'm comparing it with plaintiff's trial Exhibit 574. And I'm just getting an explanation as to how the numbers on 574 correlate to the 1547. Go ahead.

THE WITNESS: We have everyone here. So that this pattern just gives an extract from the positions 5214. And this list starts longer.

THE COURT: So this is one segment, then these numbers?

THE WITNESS: That's the complete list, yes. And when you come to a position for example when you're close to between 14 and 15, the numbers get higher. So now 15.0 it

might be this position and then a bit higher.

THE COURT: So, a very high number will show the peak?

THE WITNESS: Correct.

THE COURT: Okay.

THE WITNESS: You can see that better in the X Y derived from that.

THE COURT: In the other chart?

THE WITNESS: In the other chart because like you have on the left side something like 14 or 15 and then you see that the numbers are increasing there. Not on this, because it's just the beginning of the files.

THE COURT: I understand this is --

THE WITNESS: This pile, it must be --

THE COURT: So it would be somewhere in the middle.

THE WITNESS: Like here.

THE COURT: I can see from these are much higher.

THE WITNESS: Yes, 14.5 you have 3283. It's like how do you call it the stock, like the stock.

THE COURT: I understand that. All right. Sounds good. So that helps me out. Thank you. I was just trying to read the two together.

MR. ALY: Thank you very much, your Honor. For the record, that was page 15044 that the witness had used as an

example.

THE COURT: Thank you.

Q. Just to close us out, Dr. Gruss, this is the XRPD data for patch 0. Is that right?

A. That's my understanding.

Q. Let's bring up another pair which is plaintiff's Exhibit 577 and 605. Do you recognize these documents?

A. Yes, as well

Q. What are these?

A. This is also second x-ray diffraction pattern of Number 0 as I recall.

Q. Second recording, is that what you said?

A. Yeah, that is what I, how I understand it.

Q. Second run?

A. A second run most likely on the same sample. I am not sure about that because I did not do the experiment by myself.

Q. Let's now turn to one more pair. This will be the last one, I promise.

Plaintiff's Exhibits 608 and 612.

A. Okay.

Q. Do you have those documents?

A. Yes, I have them.

Q. Do you recognize these exhibits?

A. Yes.

Q. What are they?

A. That's also data from batch 0 records had one day later at university of Aachen as well.

Q. Another XRPD on batch 0?

A. Yes.

Q. Okay. You can set those down.

Was there a single department that was the source of the samples of Tapentadol that you collected?

A. No. Although we had samples coming from various departments at that point in time because during the course of time, investigations have been made in various departments on Tapentadol hydrochloride.

Q. Did you prepare a slide today that shows some of those departments?

A. I helped to prepare a slide.

Q. Helped to prepare a slide. Can we see that slide? Is this that slide, doctor?

A. Yes.

Q. Can you give the Court a brief overview of the departments that were the source of the Tapentadol samples?

A. Yes. On the left-hand side you see the medicinal chemistry that was in former times called synthetic chemistry. There was Helmut Buschmann lab head and afterwards heads of synthetic chemistry and medicinal chemistry. And on the right side above is the chemical development department, it's abbreviated with CE stands for German word chemische

entwicklung which is translated as chemical development.

And then we have Wolfgang Hell. And below is process development department. First there is Michael Finkam, later was Oswald Zimmer. And in that department my laboratory was afterwards located. And below will be the analytical chemistry.

First when I joined Grunenthal head person was Oswald and after Michael Finkam moved from process development to analytical chemistry, did rounds and proceeded to the other departments.

During the course of development there's a general investigation began of synthetic chemistry. This is the original investigation search of compounds and molecules. And later on for the development processes other capabilities and facilities are needed to scale up.

So generally in medicinal chemistry just tiny amounts of material is prepared, maybe up to one gram or so depends. And then later on in the other departments the scale up to bigger batch slides kilogram or a hundred grams or 10 grams scale. Maybe it advances down.

Q. Which department was batch 0 from?

MR. ALY: Objection, lack of foundation.

THE COURT: You can further ask. Go ahead.

Q. Do you know which department batch 0 came from?

A. To my understanding I was not at the company at this

point in time.

MR. ALY: Objection renewed, your Honor.

THE COURT: You can do a little foundation on that. So go ahead.

A. So from my understanding that was made in medicinal chemistry department, the laboratory of Helmut Buschmann.

Q. What is the basis for your knowledge that it came from the medicinal chemistry department?

A. As far as I remember I have seen a protocol of preparation of form of batch 0 once. And there have been presentations for example as far as I remember in the company where the history of the Tapentadol was shown.

Q. Were any batches from process development tested?

A. Yes, as well later on that we have generated samples and the samples have also been tested.

Q. Do you recall what polymorphic forms were present in the samples from process development?

A. It was A. It was B. It was mixtures of A and B.

Q. Were any batches from the chemical development department tested?

A. Sorry, could you repeat.

Q. Were any batches from chemical development tested?

A. Yes as well.

Q. Do you recall what polymorphic forms were present, I'm sorry, in the samples from chemical development.

A. Yeah, it was B. It was A. And it was mixtures of A and B.

Q. Let's bring up plaintiff's Exhibit 668.

A. Can I have some more water?

THE COURT: Yes.

Q. Let's also bring up column 20.

Do you recognize this document, doctor?

A. Yes.

Q. What is this?

A. It's the United States patent, patent number U.S. 6,248,737 B1.

Q. You're not mentioned on this patent as inventor on the patent, correct?

A. That's correct. I'm not an inventor on that patent.

Q. Do you see example 25 in column 20?

A. I see it.

Q. Do you recall anyone at Grunenthal attempting to resynthesize example 25?

A. Yes.

Q. Do you recall who conducted that resynthesis?

A. Yes, as far as I remember that was Marita Mueller under the supervision of Constan Leber (ph).

Q. What department were they in?

A. Process development department.

Q. What is Miss Mueller's position at Grunenthal?

A. To my knowledge she was a technician.
Q. And were Miss Mueller's samples sent out for XRPD analysis?
A. Since we hadn't had our own facilities with respect to x-ray powder diffraction, yes.
Q. Yes, they were?
A. Yes, they were.
Q. Let's turn to plaintiff's Exhibits 1580. Do you have Exhibit 1580, doctor?
A. I'm on 1580.
Q. Do you recognize this document?
A. Yes. That's the translated version. Do we have the original one?
Q. You want to see the original one? It's at PTX 563.
A. Sorry, which number was it?
Q. 563.
A. Yes.
Q. Okay. Do you recognize this exhibit?
A. Yes.
Q. What is this exhibit?
A. This is an exhibit of about sending a sample to university of Aachen of CG503. And that's a typo in the translated version because the version says just CG.
Q. Let's bring up that row here. This is the translated version that's on your screen?

A. Yeah, right. And in the original version on the left side it's CG5503 which is a synonym for Tapentadol hydrochloride.

Q. Just so we're clear, the typo here you are looking at CG503. Is that right?

A. Correct.

Q. What should that actually read?

A. Sorry.

Q. What should it say?

A. It should read CG 5503 like in the original German version.

Q. It's correct in the German version?

A. It's correct in the German version.

Q. So what sample is being sent out here?

A. Samples called GBBU 322 minus one minus one HCL.

Q. What sample is that?

A. My understanding is this is a sample from the resynthesis.

Q. From Marita Mueller's resynthesis?

A. Yes.

Q. And did you review the results of the -- did you review the XRPD data from Marita Mueller?

A. Did I review the results?

A. As far as I remember, yes.

Q. Did you reach a conclusion?

A. Yes.
Q. What is your conclusion?
A. The result of the resynthesis of example 25 was form B.
Q. Let's go now to the next slide which is 491C.
A. Do I need this?
Q. You don't need that.
A. Okay. So I will put it back.
MR. CONNOLLY: Can I just ask the witness to move the microphone closer?
THE WITNESS: I cannot sing otherwise I would love to.
MR. CONNOLLY: I will respond with the only German I know, yah.
(Laughter)
Q. Do you have plaintiff's trial Exhibit 491?
A. Let me go to the page.
Q. The first page.
A. I'm on 491.
Q. For the record this first page is GRTNUC 00056667. Do you see that?
A. Yes, 56667.
Q. Do you recognize this exhibit?
A. Yes.
Q. What is this exhibit.
A. It's a representation so it shows two patterns. The

bottom pattern is a calculated stray powder diffraction of BN 200 hydrochloride Tapentadol hydrochloride form B. And the pattern above is the pattern from the resynthesis of the example 25.

Q. How do you know that the top pattern is showing the resynthesis?

A. After the BN 200 HCL it says GBBN 200/patent.

Q. And BN 200 that's referring to the Tapentadol hydrochloride?

A. BN is a synonym for Tapentadol hydrochloride.

Q. Looking at this pattern, can you reach any conclusion as to the polymorphic form of Marita Mueller's resynthesis?

A. The resynthesis of example 25 of the composition of meta patent is form B.

Q. Do you see any form A here?

A. I don't see any form A.

Q. Is that consistent with your memory of the results at the time?

A. Yes.

Q. Let's now go ahead to 56668.

A. Sorry.

Q. Is this 491? Let's bring up 491C.

A. Can you point me again to the --

Q. Are you in 491C, doctor?

A. No, not anymore. It's 668.

Q. Yes, 668.
A. Okay. I'm on.
Q. Do you recognize this page, doctor?
A. Yes.
Q. What is being shown here?
A. It's a comparison of two x-ray powder patterns where the lower pattern is a calculated pattern of form A and the above pattern is a pattern from the resynthesis.
Q. Is it from the same resynthesis by Marita Mueller?
A. No. I think that was from a second run.
Q. And in this case it's being compared to form A. Is that right?
A. Correct.
Q. Can you reach any conclusion from this page?
A. Yes, there is no form A in the resynthesis pattern.
Q. What form do you believe this resynthesis to be?
A. That must be form B.
Q. And is that consistent with your memory of the results at the time?
A. Yes.
Q. Pure form B. Is that right?
A. I don't see any A in that.
Q. Are the dates for the -- did you help to add the dates for batch 0 and the resynthesis to your timeline?
A. Yes.

Q. Is this that timeline doctor?
A. That's it.
Q. And was a patent filed on your invention?
A. Eventually, yes.
Q. Let's go to the patent one more time if we could. It's 1458. If you look at the cover page, this page here, actually not the cover page, the first page of the patent.
A. Yes.
Q. Do you see a foreign application priority date?
A. Yes.
Q. Let's go back to the next page.
A. Not on that page.
Q. What is the foreign application priority date indicated here?
A. June 28, 2004.
Q. Did Grunenthal conduct clinical trials on Tapentadol in the United States?
A. To my knowledge, yes.
Q. Were you involved with those clinical trials?
A. No, I was not involved and I was not responsible for clinical trials at Grunenthal.
Q. In regard to Tapentadol, your area of focus was polymorphism studies. Is that right?
A. Right.
Q. Do you know if the dosage forms of Tapentadol used in

the studies were analyzed to see which polymorph forms were present?

A. Could you please repeat.

Q. Sure. Do you know if the dosage forms of Tapentadol used in the U.S. clinical studies were analyzed to see which polymorph forms were present?

A. To my knowledge they have not been investigated with respect to polymorphism.

Q. Do you know if a specific material used to prepare the dosage forms for the U.S. clinical trials was tested for polymorphism?

A. Not to my knowledge.

Q. Do you have an understanding of why it was not tested?

A. As far as I know and as far as I remember, there hasn't been a specification in place that required testing against polymorphism in that point of time.

Q. Now the APPI used to prepare those dosage forms would have come from a larger batch in Germany. Is that right?

A. That is my understanding.

Q. Do you know if any samples taken from those larger batches in Germany were analyzed to determine the polymorphic form?

A. To my knowledge, as far as I remember and to my understanding there has been samples derived from that bigger batch. And that samples have been handled in Germany and have

been tested in Germany with respect to polymorphism.

Q. And would that reveal then the polymorphic form of the dosage forms distributed in the United States?

A. No.

Q. Would that reveal a dosage form of a specific material used to formulate the dosages in the United States?

A. No.

Q. Why not?

A. Because the material has gone different ways. So the examples have been derived from a bigger batch and have been transformed, no not transformed, how you call it, relocated, moved from the production to the analytical department. And they might have been handled in the uncontrolled way. Because as far as I know, there has been no obligation to handle them specifically.

They might have been started for example and they might have been tested material that have eventually applied in the United States is another part of the bigger batch that has been shipped to the U.S., has been formulated in the U.S. And then the formulated substance, drug product has been then transferred to the clinical trial centers.

So, different ways, different locations where the samples are. And then different procedures which might, which have the samples might have been undergone by this formulation step. This could have changed.

Q. It could have changed?
A. Could have changed.
Q. The polymorphic form?
A. Could have changed, yeah.
Q. Sitting here today, do you know what form of Tapentadol was used in the 2001 2002 clinical trial?
A. No. Could have been B. Could have been A. Could have been mixture A and B.
Q. Did you ever know what was used in those forms?
A. No.
Q. Let's stay with the patent here. We covered a little of this already but could you summarize what you see as each of your team members' contribution to this invention?
A. Okay. The first Helmut Buschmann, I think you met him already. Let me start with, so he had the vision that the systematic investigation of polymorphism must be performed also on Tapentadol. So that was the reason why he hired me. He contributed also to phone conferences and discussions about the polymorphism.

Andreas Fischer, at that point in time when I joined, as I mentioned, he did external investigations. He determined the x-ray crystal structure of Tapentadol hydrochloride. Later on when he joined Grunenthal, he also participated in discussions, phone conferences like Helmut.

And Dagmar as well Lischke did some early

investigations on some of the behavior of the Tapentadol hydrochloride. And she was also involved in discussions about the project and phone conferences with SSCI as far as I remember.

I myself put together the samples. I added the additional, the knowledge about the additional analytical technique like XRPD to that, put the data together. And furthermore was project lead for the corporation with SSCI at that point in time and did additional polymorphism studies on Tapentadol. And also contributed to phone conferences and discussions of course and drew the conclusions that let us eventually understand that there are two forms.

Q. You are aware of the structure of the Tapentadol when you started your investigation. Is that right?

A. You mean the chemical structure?

Q. Yes, the chemical structure.

A. Yes.

Q. Could the polymorphism of Tapentadol have been predicted from the chemical structure?

A. Not to my understanding it could have not been predicted at that point in time.

Q. Let's go to column 1, Line 58 to the bottom of that column. Column one, doctor, in the patent.

A. It's 598. Okay.

Q. Can you go to the paragraph down here. It's the

bottom most paragraph. Do you see a sentence there starting with the present invention?

A. Yes.

Q. Could you read that sentence and read the one that follows it?

A. The present invention provides a new form and references form A of chemical name of Tapentadol hydrochloride which is different from the already known form B obtained by the procedure described in example 25 of U.S. patent Number 6,248,737 and U.S. patent Number 6,344,558 as well as European patent 693475 B1.

And the next sentence as well? This new format of the chemical name of Tapentadol hydrochloride is very stable at ambient conditions and therefore useful for producing a pharmaceutical composition.

Q. In your opinion are those accurate statements of invention of the '364 patent?

A. Yes.

MR. SCHULER: Your Honor, he is not an expert. He shouldn't be asked opinions. He can recite his understanding. He's been phrasing the question as an opinion.

THE COURT: I think he is telling us his understanding. I understand your objection. And again since it's a bench trial, I will be able to listen to the experts as well as those who are the inventors and other witness and sort

it out.

Go ahead.

MR. GLANDORF: No further questions. I have thank you, Dr. Gruss.

THE COURT: All right. Thank you. You are free for today. We will see you tomorrow morning. Remember that you are going to remain under oath. So, to the extent, you know, you're going to be speaking with counsel, you are not to speak of your testimony here today which --

THE WITNESS: But, I can speak with Counsel?

THE COURT: Yes, you can talk with Counsel. I am sure they would be happy to make arrangements for you this evening because you will be back tomorrow. We are going to be starting at 8:30 tomorrow morning. But otherwise, yes counsel.

MR. ALY: Yes, your Honor. May I also ask that the witness not speak with Dr. Buschmann while he is under examination.

THE COURT: Is Mr. Buschmann home already?

MR. SITZMAN: He is on his way.

THE WITNESS: Can I speak with him about private stuff?

MR. ALY: If the Judge allows you, I have no objection.

THE COURT: You have no objection. That's fine as long as you don't speak about the matters of your testimony

and the matters of this case, that will be fine.

THE WITNESS: I just want to say goodbye.

THE COURT: That will be fine. I don't think anyone has any objection to that.

We will see you tomorrow morning. Again, I've given you sort of an indication as to what happens with respect to the oath. It will remain in place until tomorrow morning and we completer your testimony. And again I am hopeful it is tomorrow morning, but we will see how that goes.

In any event, thank you very much. Thank you everyone. We will see the entirety of you at 8:30 tomorrow morning.

(Whereupon the matter was concluded)